FORMULATION AND EVALUATION OF TRANSDERMAL PATCHES OF ATORVASTATIN CALCIUM

Dissertation work submitted to

THE TAMIL NADU DR. M.G.R. MEDICAL UNIVERSITY, CHENNAI

In partial fulfillment of the award of degree of

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Submitted by
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Under the guidance of

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Coimbatore – 641044

CERTIFICATE

This is to certify that the dissertation entitled **"FORMULATION AND EVALUATION OF TRANSDERMAL PATCHES OF ATORVASTATIN CALCIUM"** *was carried out by* **Mr. M. RAJA OMAR SHERIFF,** *in the Department of Pharmaceutics, College of Pharmacy, Sri Ramakrishna Institute of Paramedical Sciences, Coimbatore, which is affiliated to the Tamilnadu Dr. M.G.R. Medical University, Chennai, under the direct supervision and guidance of* **Prof. M. Gopal Rao, M.Pharm.,(Ph.D.),** *Department of Pharmaceutics, College of Pharmacy, SRIPMS, Coimbatore.*

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"The dream is not what we see in sleep,

Dream is the thing which does not let us sleep"

Dr. A. P. J. Abdul Kalam.

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CONTENTS

INTRODUCTION

This century has witnessed several spectacular developments in the field of pharmaceutical sciences especially in the drug delivery systems. The newer drug delivery technology has received an increasing attention in the face of growing awareness that drugs are excessively toxic and sometimes ineffective, when administered or applied by conventional means. Thus, conventionally administered drug formulations such as tablets, capsules, injections and oral liquids that are administered as multi-doses usually produce large fluctuation of drug concentration in the blood stream.

The impetus for the development of newer drug delivery system, apart from therapeutic efficiency, is the cost. The developmental cost of a new drug may be about $250 millions (Rs. 900 crores) and takes about 12-15 years to reach the market. An existing drug molecule can be developed as a newer drug delivery system in half the time, with 20% cost of new drug discovery.

A wide variety of newer drug delivery systems have been designed and evaluated. This technology is applicable to many type of pharmacological agents and in many therapeutic situations, namely hypertension, asthma, arrhythmias, diabetes, fertility control, peptic ulcers, rheumatoid arthritis, angina pectoris, cancer, depression, menopausal syndrome etc. newer drug delivery systems represent a means by which a pharmacologically active moiety may be continuously delivered either systemically or to a target site in an effective, reliable and safe manner. They are capable of better performance than conventional delivery by monitoring the concentration, location and duration of drug action.

Historic development of T.D.D.S

The potential of using intact skin as a part of drug administration to the human body had been recognized long back as evidenced by development and extensive use of medicated plaster for many decades. Historically, the medicated plasters could be viewed as the first application of the idea of Transdermal drug delivery, bringing medication into close contact with the skin, through which drug is delivered trandermally[1]. The use of medicated plasters could be traced several hundred years back to ancient china. Several Chinese medicated plasters are still available even today in the market and regularly used for medical treatment. This early generation of medicated plasters often contains a combination of extracts from several herbal drugs, which are used mainly for localized medication.

The medicated plasters have also been very popular in Japan and may are available as over the counter (OTC) pharmaceutical dosage forms, commonly called cataplasms.

Medicated plasters had also existed in western medicine for several decades. In the United States, the following three medicated plasters have been listed in official compendia (NF 1946, USP 1950) namely belladonna plaster (local analgesic), mustard plaster (local irritant) and salicylic acid plaster (keratolytic agent). These plasters are rather simple in formulation and were development mainly for local medication.

Development in transdermal drug delivery

The skin was though to be an impervious barrier. At the turn of the century, during world war II, munitions workers experienced fewer anginas attacks while working with nitroglycerin. This has challenged the traditional belief that the skin is a perfect protective barrier and also triggered intensive research activities to study the feasibility of transdermal drug delivery for

systemic medication[2, 3].

Several transdermal drug delivery systems (TDDS) have recently been development with the aim of accomplishing the objective of systemic medication through the transdermally controlled delivery of pharmaceuticals. The potential of TDDS was first demonstrated by the successful development of a scopolamine releasing TDD system in 1981 (Transderm- Scop system, Ciba) for 72-hour prophylaxis or treatment of motion induced sickness and nausea, then by the marketing success of several nitroglycerin releasing TDD systems of once – a- day medication of angina pectoris[4], Clonidine – releasing TDD systems for weekly therapy of hypertension[5] and Estradiol- releasing TDD systems for twice a day week treatment of post menopausal syndrome[6]. The other marketed TDD systems are given in the table-1.

In addition to the currently marketed formulations, new drugs are being formulated using transdermal systems because of the inherent advantages of administration by this route. Buspar, an anti anxiety agent and the combination of nicotine and mecamylmine, for smoking – cessation therapy are being developed for TDDS and are currently undergoing phase III clinical trials.

Skin structure and barrier properties

Skin is the most readily accessible organ in the body. Its chief functions are protection, temperature regulation, control of water output and sensation. The skin of an average body covers a surface area of approximately 2 sq. mts. in most adults, varying in thickness from approximately 1.5 to 4 mm and weighing approximately 2 kg.

Table – 1: Commercially available transdermal therapeutic systems

Drug /Manufacturer	Trade Name	Duration	Type of System	Therapeutic use
Scopolamine -Alza/Ciba	Transder • Scop	2 days	Reservoir	Alleviate Motion Sickness
Nitroglycerin				
Alza/Ciba	Transderm• -Nitro	1 day	Reservoir	Treatment and prevention
Hercom	NTS•		Matrix	Of angina
Searle	Nitrodisc•		Matrix	
Key	Nitro-dur•		Matrix	
Wyeth	Deponite •		Sandwich	
Isosorbide dinitrate				
Nitro – electric industrial	Frandol Tape •	1 day	Matrix	Treatment and prevention
Clonidine				Of angina
Boehringer/Ingelheim	Catapres-TTS•	7 day	Reservoir	Treatment of hypertension
Estradial				
Ciba –Geigy	Estraderm•	3 day	Reservoir	Relief of post menopausal Symptoms
Nicotine				
Alza	Nicoderm•	1 day	Reservoir	Aid is smoking cessation
Ciba –Geigy	Habitrol •		Matrix	
Parke –Davis	Prostep•		Matrix	
Fentanyl				
Janssens	Duragesic •	3 day		Relief from moderate/ severe pain

- Information not available
- This product is available in India (Transderm-TTS; CIBA-GEIGY; Top nitro FULFORD (India)]

- This product is very recently launched in India.

It receives about one third of the blood that is circulating through the body[7]. Skin consists of two parts; the cellular outermost layer, epidermis and the relatively a cellular connective tissue matrix dermis (Figure:1) Lying between these two layers is a sub- microscopic structure, the basal lamina, which is derived from both the epidermis and the dermis. It serves as an anchoring structure by which the two layers of skin are held together. The blood supply to the skin resides exclusively in the dermis and the nutritional requirements of the epidermis are met by diffusion.

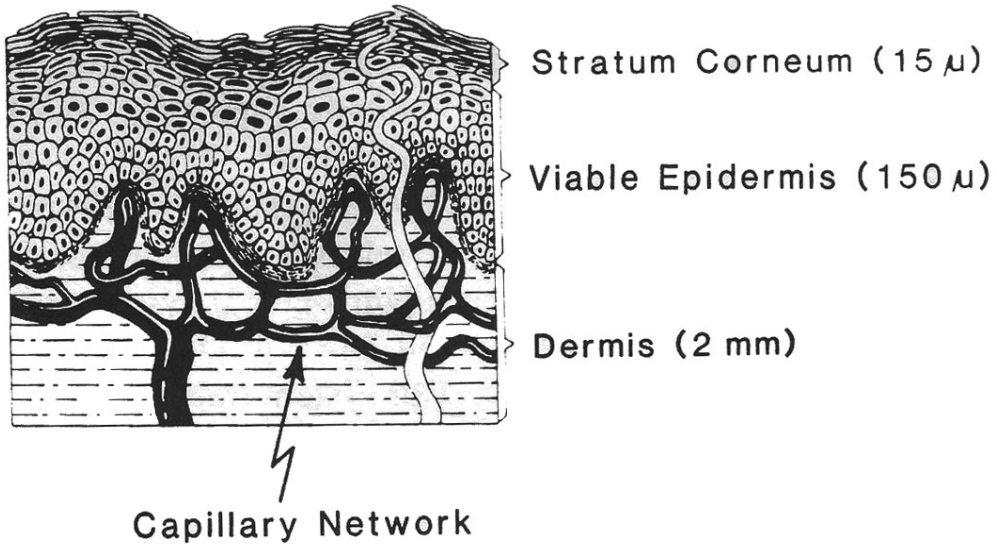
The epidermis is composed of two parts: the living cells of the malphygian layer and the dead cells of the horny layer (stratum corneum). Epidermis is composed of four cell types; keratinocytes, which constitutes approximately 80% of the epidermis; melanocytes, the source of the melanin pigment which gives the skin gets its colour and protects form the damaging effects of UV radiation; langerhans cells, which are the outmost arm of the immunologic system and serve in host defense; merkel cells, which are thought to function as mechanorecptors for the sensation of tough. Keratinocytes organize into strata within the epidermis form inside to outside, stratum germinatum, stratum spinosum and stratum corneum.

The stratum corneum typically comprises 10 to 15 cell layers and is approximately 10mm thick when dry. This membrance consisting of dead, anucleate, keratinized cells embedded in the lipid matrix, is essential for controlling the percutaneous absorption of most drugs and chemicals. The barrier nature of the horny layer depends critically on its constituents, 75-80% proteins, 5-15% lipids and 5-10% unidentified material on a dry weight basis[8]. The protein fraction predominantly comprises of keratin filaments which are cross – linked by inter molecular disulfide bridges[9]. The lipid domain is comprised of an organized distribution of intercellular lamellae derived form intra cellular granules secreted during the epithelial

differentiation process[10].

The dermis is 3 to 5 mm thick and is composed of a matrix of connective tissue in which predominant bundles of collagen fibrils interlace with elastic tissue and sparse reticular fibers[8]. The dermis encloses cutaneous appendages (eccrine sweat glands, apocrine gland and pilosebacious units) and is penetrated by blood vessels, lymphatics and nerves.

Figure 1. Simplified structure of human skin, with potential routes for drug permeation indicated.



The blood supply thus keeps the dermal concentration of a penetrant usually very low and the resulting concentration difference across epidermis provides the essential driving force for transdermal permeation.

The fatty subcutaneous tissue merges with the over-lying dermis. The hypodermis supplies a layer of adipose tissue over most of the body that provides thermal insulations & mechanic protection. It carries the principal blood vessels and nerves to the skin and may contain sensory pressure organs.

Fundamentals of skin permeation.

A systematically active drug that will reach a target tissue for from the site of drug administration of the skin surface must posses some physico-chemical properties that are capable of facilitating the sorption of drug through viable epidermis and also uptake of the drug by capillary network in the dermal papillary layer. The sequence of transdermal permeation of the drug is shown in Fig.2.

The rate of the permeation, dQ/dt across the skin tissues can be expressed mathematically by the following relationship[11].

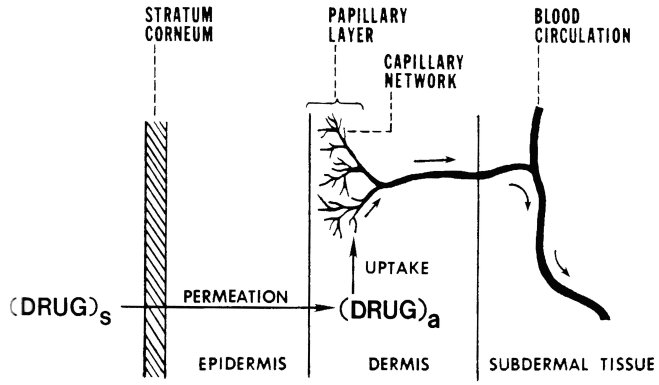
$$dQ/dt=p_s\,(c_d-c_r)\text{----------(1)}$$

Where c_d and c_r, respectively the concentrations of a skin penetrant in the donor compartment (e.g., the drug concentration of the surface of the stratum corneum) and in the receptor compartment (e.g. Body). P_s is the overall permeability coefficient of the skin tissues to the penetrant as defined by

$$P_s=K_s\,D_{ss}/h_s$$

Where K_s is the partition – coefficient for the interfacial partitioning of a penetrant molecule form the solution medium or a transdermal therapeutic system on to a stratum corneum; D_{ss} is the apparent diffusivity for the steady state diffusion of the penetrant molecule through a thickness of skin tissues; and h_s is the overall thickness of the skin tissues.

Figure 2: Multilayer skin model showing the sequence of transdermal permeation of drug



Analysis of eq. 1 suggests that to achieve a constant rate of drug permeation one needs to maintain the drug concentration on the surface of stratum corneum (C_d) consistency and substantially greater than the drug concentration in the body (C_r) i.e., $C_d > C_r$; under such a condition eq.1 can be reduced to

$$dQ/dt = P_s C_d$$

The rate of skin permeation dQ/dt becomes a constant, if the magnitude of C_d remains fairly constant throughout the course of skin permeation. To maintain C_d at a constant value, it is necessary to make drug release at a rate (R_d) that is either constant or always greater than the rate of skin uptake (R_a) i.e., $R_d > R_a$. By making R_d greater than R_a, the drug concentration on the skin surface (C_d) is maintained at a level equal to or greater than the equilibrium (or saturations) solubility of the drug in the statum corneum (C_{se}) i.e., $C_d > C_{se}$, and a maximum rate of skin permeation $(dQ/dt)_m$, as expressed by equation (2) is thus achieved.

$$(dQ/dt)_m = P_s C_{se} \text{ ----------(2)}$$

The other mechanism of permeation involves diffusion through

shunts particularly those offered by the relatively widely distributed hair follicles and eccrine glands[12]. Typically one square centimeter of human skin yields 10 hair follicles, 15 sebaceous glands and 100 sweat glands. However, the appendages provide a small fractional surface area of approximately 0.1% of the total area.

Recent studies[13] indicate the importance of appendages in percutaneous absorption. The appendageal route may be more significant for ions and large polar molecules[14], which slowly permeates through intact stratum corneum. The major fraction of most diffusants permeates across the bulk of the intact horny layer. The two potential micro pathways serve the stratum corneum through the transcellular and intercellular routes.

The principal pathway taken by the penetrant is decided mainly by diffusants's partition coefficient. Most of the diffusants permeate by both the routes[15]. The intercellular pathway is considered to provide the principal route and the major barrier to the permeation of the most drugs[16].

Technologies of transdermal drug delivery systems

Several techniques have been successfully developed to provide a mechanism of rate control over the release and transdermal permeation of drugs. To be precise, there are two concepts in the design of TDDS namely skin controlled device (monolith type) and system controlled device (reservoir type). The others are extension of these two concepts.

Skin controlled device: (Monolith or Matrix System)

It is designed to rely on the skin to control the rate at which drug diffuses into the body. Skin controlled devices are typically monolith systems that incorporate a drug in matrix layer between frontal and backing layers. The polymer matrix controls the release rate (Proportional to the square root of time), Which is generally greater than the permeation rate

across the skin.

System controlled device: (Reservoir or Membrane System)

The transdermal system providers the majority of the control of the rate of drug input to the body. System controlled devices contain a rate controlling membrane and the drug (usually in liquid or general form) is in a reservoir, backing, adhesive and protective layers are other functional components of the system. This type of system is beneficial when the desired rate of drug transport is considerably less than that through the skin.

Polymer membrane permeation – controlled systems

In this system, the drug reservoir is encapsulated in a compartment molded from a drug impermeable backing layer and a rate controlling polymeric membrane (Fig. 3.a.). In the drug reservoir compartment, the drug particles are either dispersed in a solid polymer matrix or suspended in an unleachable, viscous liquid medium. On the external surface of the Polymeric membrane, a thin layer of drug compatible adhesive polymer e.g., silicone or polyacrylate adhesive, is applied to provide an intimate contact between device and skin surface. Several TDDS formulations have been marketed from this technology e.g.

- Transderm – Scop (Ciba /Alza)
- Transderm – Nitro (Ciba / Alza)
- Estraderm (Novartis)
- Nicoderm (Alza)
- Catapress – TTS (Boehringer/ Ingelheium)
- Duragestic (Janssens)

Matrix diffusion - controlled systems

The drug reservoir in this type of devices is formed by

homogeneously dispersing the drug particles in a hydrophilic or lipophilic polymer and the medicated polymer is then molded into a medicated disc with a defined surface area and thickness. This medicated disc is then glued to a base plate, which is sealed to a drug impermeable backing (Fig.3.b). Most of these systems do not have an adhesive overlay but instead posses a peripheral adhesive ring. e.g

- NTS (Hercom)
- Nitro – dur (Key)
- Prostep (Parke – Davis)

Adhesive diffusion controlled systems

In this, the drug reservoir is formulated by directly dispersing the drug in an adhesive polymer on a flat sheet of drug impermeable backing to form a thin drug reservoir layer (Fig. 3.c). Layers of non-medicated rate controlling adhesive polymer of constant thickness (Fig.4C) are applied to produce an adhesive diffusion – Controlled drug delivery system. e.g

- Deposit (wyeth/Schwartz)
- Frandoltape (Toaeiyo)
- Minitran (3M Riker)
- Habitral (Novartis)
- Nicotinell (Novartis)

Micro reservoir / micro sealed controlled systems

These systems are a combination of the reservoir and matrix dispersion type drug delivery systems (Fig 4d). In these systems, drug dispersion is prepared by suspending the drug in an aqueous polymer solution and then the drug suspension is dispersed homogeneously into lipophilic polymer by high shear mechanical force, to form microscopic spherical reservoir with the drug entrapped. This unstable dispersion is

stabilized by cross- linking the polymer chains by the addition of polymeric cross – linking agents. This matrix is then attached to an adhesive foam (flexible) backing. The System has a peripheral adhesive ring.

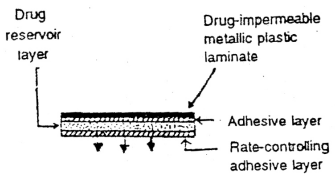
Eg. Nitro disc (G.D. Searle)

Advantages and limitations of T.D.D.S

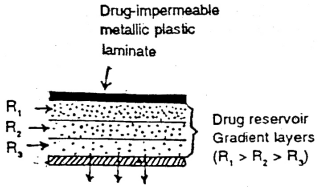
Advantages of TDDS

- Avoids vagaries associated with gastro – intestinal absorption due to pH, enzymatic activity, and drug food interactions.
- It is a substitute for oral route
- Avoids first pass effect (drug deactivation by digestive and liver enzymes)
- It avoids the risks and inconveniences of i.v therapy
- Provides predictable extended duration of activity
- Extends the activity of drugs with short half – lives
- Multi day therapy with single application
- Provides capacity to terminate drug effects rapidly
- Rapid identification of medication in emergency eg., non-responsible, unconscious or comatose patients.
- Minimize inter and intra patient variation
- Provides suitability for self-administration.
- Reduces daily dosing, thus improving patient compliance.

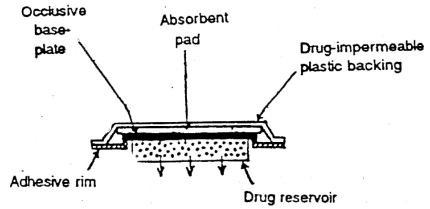
Figure 3: Different Types of transdermal delivery systems



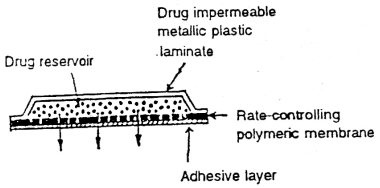
Adhesive-dispersion type transdermal drug delivery system.



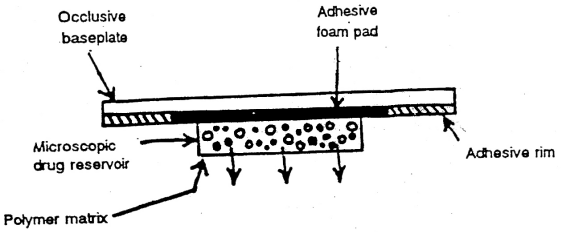
Drug reservoir gradient-controlled transdermal drug delivery system



Cross-sectional view of matrix diffusion controlled transdermal drug delivery system showing major structural components.



membrane-moderated transdermal drug delivery system.



Microreservoir dissolution-controlled transdermal drug delivery system.

Limitations of TDDS

- TDDS cannot be used for the drugs
- Limited time that the patch can remain affixed
- Variable intra- and inter individual percutaneous absorption efficiency.
- Skin rashes and sensitization.
- Bacterial and enzymatic drug metabolism under the patch
- Complex technology / high cost

MATERIALS AND COMPONENTS

The various materials used in TDDS are on the basis of functional classification of the various components. The basic components of transdermal devices are polymeric matrices or reservoirs, drug, permeation enhancers and other excipients.

Polymers for transdermal delivery

The polymer controls the release of the drug from the device. The following criteria should be satisfied for a polymer to be used to a transdermal system.

- Drug solubility and diffusivity in the polymer.
- The desired drug loading and its effect on polymer integrity.
- Compatibility of the polymer with necessary excipients, such as solvents and skin permeation enhancers for the drug.
- Skin compatibility: the effect of moisture occluded under the polymer formulation.
- Mechanical properties: softness, flexibility, conformability to skin and mechanical integrity.
- Ease of fabrication.

- Toxicity and purity i.e., compliance with safety requirements of the FDA.
- Cost and availability.
- It is rare to find a commercial polymer that satisfies all the above criteria for polymer selection. Hence various techniques have been employed to modify the polymer properties and thus drug – release rates.
- Cross linked polymers: The higher the degree of cross-linking, the more dense the polymer and slower the diffusion of drug molecules through the matrix cross – linking may be achieved chemically using cross – linking agent or by irradiation. This approach has been applied to the preparation of the nitro disc system[17, 18].
- Polymer blends: The blended polymer combines the advantages of individual polymers. The potential advantages include easy fabrication of devices, manipulation of drug loading and other device properties such as hydration, degradation and mechanical strength.
- A number of patents have covered the use of PVA & PVP blends but only nitro- dur System has been commercialized and marketed. The system was fabricated from polymeric matrix made of PVA, PVP & glycerol as plasticizer. The selected patented polymer blends of PVA & PVP are given in the table.

Patented blend formulations of PVA & PVP for matrix devices[19, 20, 21].

Sl. No	Patent No	Drug	Recipe (%)
1)	4,438,139	Estrogen	1-60 Plasticizer 6-30 PVA 2-30 PVP
2)	4,542,013	Nitro Glycerin	2-25 Plasticizer 10-40 PVA 2-15 PVP
3)	4,460,562	Propranolol	1-60 Plasticizer 6-30 PVA 2-30 PVP

Plasticizers: Plasticizers are used to reduce the stiffness of the polymer backbone there by increasing the diffusion characteristics of the drug. In selection of plasticizer, care must be taken to select a material that is biocompatible. Commonly used plasticizers are polyethylene glycol, polypropylene glycol, glycerol, dibutyl phthalate and dioctyl phthalate.

Commonly used polymers in T.D.D.S.

Polyisobutylene

Polyisobutylene[22] (PIB) is a highly paraffinic, non-polar and amorphous hydrocarbon polymer composed of essentially straight chain macromolecules. Physical properties of PIB change gradually with increasing molecular weight, the lowest molecular weight being viscous liquid. With increasing molecular weight. It forms elastometric solids. PIB is soluble in hydrocarbon solvents and insoluble in polar solvents, because of low glass – transition temperature flexibility and oxidative stability.

Poly acrylates

Copolymers of acrylic and methacrylic acid esters can be most suitable for use as drug / polymer matrix. Acrylate polymers, which are moderately polar, colorless and transparent, have excellent chemical resistance, plus thermal, light and oxidative stability.

Polysiloxanes

Poly siloxanes[23, 24] also referred to as silicones, are organo silicon polymers having si-o-si bonds along the main chain and an alkyl group (R) attached to a significant proportion of silicon atoms by silicon carbon bonds. These silicones have outstanding thermal and oxidative stability, chemical inertness and very low surface tension.

Hydrogels

Hydrogels[25, 26] are water swollen but water insoluble cross – linked networks of hydrophilic polymers. They can absorb water by more than 20% of its dry weight. Hydrogels are prepared by free radical co-polymerization of hydrophillic monomers such as 2 hydroxyethyl methacrylate, N-Vinyl -2-Pyrrolidone or acrylamide with small amounts of a di functional monomer such as ethylene glycol dimethacrylate and the polymerization is carried out in aqueous medium. The drug/hydrogel matrix can be prepared by either incorporating the drug in aqueous polymerization mixture or by a process of equilibrium of the hydrogel in a concentrated aqueous solution of the drug.

Polyvinyl pyrrolidone/ Polyvinyl alcohol.

Poly vinyl pyrrolidone[27] (PVP) is a white odorless and hygroscopic powder. It is available in different viscosity grades, identified by K value. It is soluble in water and in any organic solvent. Poly vinyl alcohol (PVA) is a cream coloured granular powder and is prepared from Poly vinyl acetates. PVA is available in different grades and the viscosity is directly proportional to its molecular weight. Both PVA and PVP are non-toxic to skin and incompatible with inorganic salts.

Ethylene vinyl acetate (EVA) copolymers

EVA is ideally suited for preparation of molecular diffusion type

membranes because their permeability properties can be varied over a wide range by changing vinyl acetate content[28, 29]. The stiffness, tensile strength and softening point decrease with increasing vinyl acetate content, while the permeability and toughness increase. EVA has been shown to be chemically stable, non-toxic and biocompatible. A wide range of EVA polymers are commercially available with a range of vinyl acetate content (4 to 60%)

Vinyl chloride polymers and copolymers

Vinyl chloride polymers[30] and copolymers useful for drug/ polymer matrix preparation include homo polymer vinyl chloride. CH_2=CH-Cl and the copolymer having a high vinyl chloride content. PVC needs plasticization in order to form a soft and flexible film suitable for transdermal patch formulation. The commonly used plasticizers are dioctyl phthalate, expoxidized soya bean oil & citric acid esters. The chemical nature, the proportion of the plasticizers and the drug loading in the plasticized polymer matrix, are the three parameters affecting the drug release and transport across the skin.

Selection of drug candidates for transdermal delivery

The choice of drugs to be delivered is almost a difficult one, and careful considerations should be given for selection of suitable drug molecule. The following are some of the desirable properties of a drug for transdermal delivery[31, 32].

Physico – chemical properties of drug

- The drug should have a molecular weight of less than 7.50
- The drug should possess balanced lipophilic hydrophilic characteristics and also have reasonable solubility in both lipid and aqueous phases. The log P value should be in the range 1-3.
- The melting point should be less than 200^{o}C
- Saturated aqueous solutions of the drug should have pH value between 5 and 9.

Biological properties of drug

The biological half-life ($t_{½}$) should be less then 5-6 hours.

- The drug should be potent with a daily systemic dose of less than 20 mg.
- The drug should not stimulate an immune reaction in the skin
- The drug must not induce a cutaneous irritant or allergic response.

Finally, in order to obtain the best candidate for transdermal drug delivery, an attempt should be made to keep the melting point as low as possible. Obviously, in some cases, there will be a compromise between optimizing both the partition and solubility parameters and incorporation of a suitable penetration enhancer[31, 33, 34, 35].

Penetration enhancers

The success of transdermal drug delivery systems depends on the ability of the drug to permeate skin in sufficient quantities to achieve required therapeutic plasma levels. Unfortunately many drugs do not possess, intrinsically, any great ability to cross the skin, and ways must be found to modify the barrier. This can be achieved chemically by the use of penetration enhancers[36] or physically by iontophoresis[37] and sonophoresis[38].

Chemical penetration enhancers

The penetration enhancers are agents that increase the permeability of the skin[39] or substances that temporarily reduce the impermeability of the skin[40]. The properties of an ideal penetration enhance are:

- Pharmacologically inert.
- Non toxic, non irritating & non allergic
- Rapid onset of action, predictable and suitable duration of action for drug used.
- Readily incorporated into the delivery system.
- Following removal of the enhancer, the stratum corneum should immediately and fully recover its normal barrier property.
- Chemically and physically compatible with the delivery system.
- Commonly used chemical enhancers are sulfoxides and Similar Compounds.

DimethylSulfoxide (DMSO)

DimethylSulfoxide (DMSO), the classic skin –permeation enhancer, is a powerful aprotic solvent. DMSO has been investigated as a skin permeation enhancer for wide range of drugs including antibiotics steroids, narcotics and salicylates[36]. The activity of DMSO is highly concentration dependent with 60% and above generally required to produce a significant effect.

Pyrrolidones

Pyrrolidones provide more activity toward hydrophilic drugs than lipophilic permeation. The permeation effect of pyrrolidones was reported to be concentration dependent. Unfortunately, despite the marked accelerant activity of the pyrrolidones for various drugs, the use of these agents may be constrained because they damage skin, especially at high concentrations.

Azone

Azone is the first molecule specifically designed as a skin penetration enhancer[44]. Chemically, it may be considered as a hybrid of a cyclic amide as in the pyrrolidones, with an alkyl sulfoxide. It has low irritancy and it active at low concentrations (typically 0.1 to 5%) and permeation can further be enhanced with the use of a cosolvent such as propylene glycol. Azone enhances the skin transport of a wide variety including steroids and antibiotics[45].

Surfactants

The effect of surfactant action upon the skin may change the physical state of water in the skin in such a way to permit greater freedom to the passage of charged, hydrophilic substances[46]. These can accelerate and increase transdermal permeation and percutaneous absorption. Their permeation promoting activity is due to the decrease in surface tension, to improve the wetting of the skin and to enhance the distribution of the drugs, among the three types of surface-active agents. Anionic laurate ions have the greatest penetration and strongest permeation promotion action[47].

The following surfactants have been reported as penetration enhancers. Sodium lauryl sulfate, sodium diactyl –Sulfo Succinate, Sorbitan mono palmitate, lauryl ether etc.

Miscellaneous enhancers

In an attempt to reduce reversibility barrier function of the stratum corneum, which is the major obstacle administration of therapeutic agents, new types of penetration enhancers like naturally occurring cyclic terpenes[48]. Few examples used as penetration enhancers are unsaturated cyclic ureas, cyclic monoterpenes, cineole, d- limonene etc,

Physical means of penetration enhancers

Iontophoresis

Trandermal iontophoresis deliver ions and charged molecules across the skin into systemic circulation at an increased rate in a controllable manner by the use of electric current[49]. Although many drugs were studied as suitable agents for trandermal iontophoresis, peptide/protein (pp) drugs are best suited for this technique. Latest reports regarding use of reverse iontophoresis[50] for monitoring the blood glucose is certainly going to steer and focus the research interests towards the development of commercially viable and acceptable formulations for PP drugs in general and for insulin in particular[51].

Sonophoresis

The effect of ultra sound on transdermal delivery of drugs is reported[52]. Ultra sound has been used to treat a wide range of clinical conditions and to transport drugs to deeper tissues in the treatment of inflammatory conditions. The movement of drugs through living intact skin and into soft tissue under the influence of an ultra sound perturbation is called sonophoresis[53]. The technique involves placing and ultra sound coupling agent on the skin over the area to be treated and messaging the area with an ultrasonic source. An ultrasonic coupling agent is simply a cream gel or oil, which maintains good contact between transducer head and skin. Recently sonophoresis has attracted lot of interest in transdermal delivery with the focus on peptide protein delivery.

Other excipients

Adhesives

The adhesive system used should be non irritating, non-sensitizing, should be compatible, adhere well to skin, easy to remove form skin without leaving traces of adhesive, should not affect drug permeation. Pressure –Sensitive Adhesives (PSA) have found application in transdermal

drug delivery because of the need to intimate contact between the trandermal system and the skin surface[55]. The adhesive bond formation involves a liquid like flow process resulting in adhesive wetting of the skin, surface upon application of pressure. When the pressure is removed, the adhesive sets in that state. The PSA is a characteristic of a visco elastic material, significantly above its glass – transition temperature. Commonly employed PSA include acrylate copolymers, polyisobutylenes and polysiloxanes. Acrylic based adhesives are less irritating than silicone adhesives and the migration of ingredients into the adhesive during storage may also be less compared to other types.

Backing layer

The backing layer must be impermeable to the drugs and other components of the device and also it should be impermeable to water vapour i.e, occlusive[56]. The most commonly used backing materials are polyester, polyethylene-coextruded films. The films can be either clear (Estraderm) Flesh coloured (Catapres –TTS) or metallized (Transderm Scop). Other non-porous plastics with similar properties could equally well be used. If the entire area under the patch is active and the patch is not excessively large, then it is probably most convenient to use an occlusive backing if the patch has a central area containing the drug surrounded by a ring adhesive and the size of the patch is relatively large, the wearers comfort may be increased by having a backing material that is non occlusive.

Peel strip

The peel Strip prevents drug loss when it has irrigated into the adhesive layer on storing and protects the finished device against contamination. The requirements for the peel strip are essentially the same as those for occlusive backing. The impermeable easily peelable films are made of polyester, foils etc[57].

Evaluation of transdermal drug delivery systems

Currently, tremendous research is going on in the evaluation of T.D.D.S. The objective of this research is often to find correlation between laboratory results (In-vitro) and the transdermal absorption experienced by living subjects, so that in-vivo experimentation may be curtailed. There is no elaborate information available in the literature on the in-vitro dissolution methodology, for transdermal patches. The various manufactures of transdermal patches (Novartis Key & Searle) employ different dissolution methods from the standpoint of quality assurance requirements. There is a definite need for the development and implementation of a single, probably universal, dissolution method to assure patch – to– patch uniform release. The aim of in-vitro experimentation in TDD is to understand and/ or predict the delivery and penetration of a molecule form the skin surface into the body. Typically, this is achieved by using a variety of skin diffusion cells and various experimental protocols. TDD can be described in three principal stages for understanding in designing of suitable in-vitro experiment[58, 59, 60].

- Delivery of the molecules to the skin Surface
- Passage of the molecule through the skin
- Delivery of the molecule into the body in- vivo = recovery of the molecule in-vitro.

HYPERLIPIDEMIAS AND STATIN THERAPY

Coronary heart disease[61] (CHD) is the cause of about half of all deaths in the United States. The incidence of CHD is correlated with elevated levels of low-density lipoprotein (LDL) cholesterol and triacylglycerols and with low levels of high-density lipoprotein (HDL) cholesterol. Other risk factors for CHD include cigarette smoking, hypertension, obesity, and diabetes. Cholesterol levels may be elevated as a result of an individual's lifestyle (for example, by lack of exercise and consumption of a diet containing excess saturated fatty acids). Hyperlipidemias can also result from a single inherited gene defect in lipoprotein metabolism or, more commonly, by a combination of genetic and lifestyle factors. Appropriate lifestyle changes in combination with drug therapy can lead to a decline in the progression of coronary plaque, regression of pre-existing lesions, and reduction in mortality due to CHD by thirty to forty percent. Antihyperlipidemic drugs must be taken indefinitely; when therapy is terminated, plasma lipid levels return to pretreatment levels.

TREATMENT GOALS

Plasma lipids consist mostly of lipoproteins-spherical macromolecular complexes of lipids and specific proteins (apolipoproteins). The clinically important lipoproteins, listed in decreasing order of atherogenicity, are LDL, very-low-density lipoprotein (VLDL) and chylomicrons, and HDL. The occurrence of CHD is positively associated with high total cholesterol, and even more strongly with elevated LDL cholesterol in the blood. In contrast to LDL, high levels of HDL cholesterol have been associated with a decreased risk of heart disease (figure 21.3). Reduction of the LDL level is the primary goal of cholesterol-lowering therapy. Recommendations for the reduction of LDL cholesterol to specific

target levels are influenced by the coexistence of CHD and the number of other cardiac risk factors. The higher the overall risk of heart disease, the more aggressive the recommended LDL-lowering therapy.

A. Treatment options for hypercholesterolemia:

In patients with moderate hyperlipidemia, lifestyle changes, such as diet, exercise, and weight reduction, can lead to modest decreases in LDL and increases in HDL levels. However, most patients are unwilling to modify their lifestyle sufficiently to achieve LDL treatment goals, and drug therapy may be required. Patients with LDL levels higher than 160mg/dL and with one other major risk factor such as hypertension, diabetes, smoking, or a family history of early CHD, are candidates for drug therapy. Patients with two or more additional risk factors should be treated aggressively, with the aim of reducing their LDL level to less than 130mg/dL.

B. Treatment options for hypertriacylglycerolemia:

Elevated triacylglycerols levels are independently associated with increased risk of CHD. Diet and exercise are the primary modes of treating hypertriacylglycerolemia. If indicated, niacin and fibric acid derivatives are the most efficacious in lowering triacylglycerols levels. Triacylglycerol reduction is a secondary benefit of the statin drugs.

DRUGS THAT LOWER THE SERUM LIPOPROTEIN CONCENTRATION

Antihyperlipidemic drugs target the problem if elevated serum lipids with complementary strategies. Some of these agents decrease production of the lipoprotein carriers of cholesterol and triacylglycerols, whereas others increase the degradation of lipoprotein. Still others decrease cholesterol absorption or directly increase cholesterol removal from the body. These drugs may be used singly or in combination.

HMG CoA reductase inhibitors:

3-Hydoxy-3-methylglutaryl (HMG) coenzyme A reductase inhibitors (commonly known as statins) lower elevated LDL cholesterol levels, resulting in a substantial reduction in coronary events and death from CHD. This group of Antihyperlipidemic agents inhibits the first committed enzymatic step of cholesterol synthesis. Therapeutic benefits include plaque stabilization, improvement of coronary endothelial function, inhibiton of platelet thrombus formation, and anti-inflammatory activity. The value of lowering the level of cholesterol with statin drugs has now been demonstrated in 1) patients with CHD, with or without hyperlipidemia; 2) men with hyperlipidemia but no known CHD; and 3) men and women with average total and LDL cholesterol levels and no known CHD.

Mechanism of Action:

Inhibiton of HMG CoA reductase:

Lovastatin, simvastatin, pravastatin, atorvastatin, fluvastatin and rosuvastatin are analogs of 3-hydroxy-3-methylglutarate, the precursor of cholesterol. Lovastatin and simvastatin are lactones that are hydrolyzed to the active drug. Pravastatin and fluvastatin are active as such. Because of their strong affinity for the enzyme, all complete effectively to inhibit HMG CoA reductase, the rate limiting step in cholesterol synthesis. By inhibiting *De novo* cholesterol synthesis, they deplete the intracellular supply of cholesterol. Potent LDL cholesterol-lowering statin drugs, followed by pravastatin and fluvastatin and then lovastatin and simvastatin.

Increase in LDL receptors:

Depletion of intracellular cholesterol causes the cell to increase the number of specific cell-surface LDL receptors that can bind and internalize circulating LDLs. Thus, the end result is a reduction in plasma cholesterol, both by lowered cholesterol synthesis and by increased catabolism of LDL. The HMG CoA reductase inhibitors, like the bile acid sequesterant cholestyramine, can increase plasma HDL levels in some patients, resulting in an additional lowering of risk for CHD. Decreases in triacylglycerol also occur.

Therapeutic uses:

These drugs are effective in lowering plasma cholesterol levels in all types of cholesterol levels in all types of hyperlipidemias. However, patients who are homozygous for familial hypercholesterolemia lack LDL receptors and, therefore, benefit much less from treatment with these drugs. It should be noted that in spite of the protection afforded by cholesterol lowering, about one-fourth of the patients treated with these drugs still present with coronary events. Thus, additional strategies, such as diet, exercise, or additional agents, may be warranted.

DRUG PROFILE

ATORVASTATIN

OVERVIEW [62]

Class

This drug is a member of the following class (es):

- Antihyperlipidemic
- HMG-COA Reductase Inhibitor

Synonyms

- Atorvastatin
- Atorvastatin Calcium

Physicochemical Properties

Molecular Weight

1209.42 (Prod Info Lipitor, 97)

Solubility

Atorvastatin is very slightly soluble in distilled water, pH 7.4-phosphate buffer, and acetonitrile, slightly soluble in ethanol, and freely soluble in methanol. Atorvastatin is insoluble in aqueous solutions of pH 4 and below. (Prod Info Lipitor(R), 2002)

Storage and stability

Store at controlled room temperature, 20 to 25 degrees Celsius (C) (68 to 77 degrees Fahrenheit (F)) (Prod Info Lipitor(R), 2004).

DOSING INFORMATION

Adult

a Diabetes mellitus type 2 - Disorder of cardiovascular system, in patients with multiple risk factors for coronary heart disease; Prophylaxis 10 mg ORALLY once daily (Prod Info Lipitor (R), 2005)

b Disorder of cardiovascular system, in patients with multiple risk factors for coronary heart disease; Prophylaxis 10 mg ORALLY once daily

c Familial hypercholesterolemia

Homozygous 10 to 80 mg ORALLY once daily (Prod Info LIPITOR(R) tablets, 2005)

d Familial type 3 hyperlipoproteinemia

10 to 80 mg ORALLY once daily; evaluate lipid levels after 2 to 4 wk and adjust doses accordingly

e Hypercholesterolemia, primary (heterozygous familial and non-familial) and mixed dyslipidemia (Fredrickson types IIa and IIb) initial, 10 to 20 mg ORALLY once daily; dosage range is 10 to 80 mg once daily; evaluate lipid levels after 2 to 4 wk and adjust doses accordingly (Prod Info LIPITOR(R) tablets, 2005)

f Hypertriglyceridemia

10 to 80 mg ORALLY once daily; evaluate lipid levels after 2 to 4 wk and adjust doses accordingly

Pediatric

a Familial hypercholesterolemia

Heterozygous, with LDL-C 160 or 190 mg/dL or more AND positive family history or 2 or more cardiovascular disease risk factors in boys and postmenarchal girls 10 to 17 yr, initially 10 mg ORALLY daily; titrate at 4-wk intervals up to MAX 20 mg ORALLY daily (Prod Info LIPITOR(R) tablets, 2005)

b Familial hypercholesterolemia - homozygous

10 to 80 mg ORALLY once daily (Prod Info LIPITOR(R) tablets, 2005)

Contraindications

- Hypersensitivity to atorvastatin
- Liver disease
- Pregnancy or lactation
- Unexplained, persistent elevation of serum transaminases

Serious adverse effects

- Rhabdomyolysis

Clinical Applications

FDA approved indications

a Diabetes mellitus type 2 - Disorder of cardiovascular system, in patients with multiple risk factors for coronary heart disease; Prophylaxis

b Disorder of cardiovascular system, in patients with multiple risk factors for coronary heart disease; Prophylaxis

c Familial hypercholesterolemia - heterozygous, with LDL-C 160 or 190 mg/dL or more AND positive family history or 2 or more cardiovascular disease risk factors

d Familial hypercholesterolemia - homozygous

e Familial type 3 hyperlipoproteinemia

f Hypercholesterolemia, primary (heterozygous familial and non-familial) and mixed dyslipidemia (Fredrickson types IIa and IIb)

g Hypertriglyceridemia

ADME

ABSORPTION

A) Bioavailability

14% (oral route) (Lennernas, 2003).

a Absolute bioavailability was 14% after a 10-mg oral dose (Lennernas, 2003).

b Atorvastatin is rapidly absorbed after oral administration in the fasting state (Prod Info Lipitor(R), 2003; Gibson et al, 1996).

B) Effects of Food

1) rate of absorption slowed (Lennernas, 2003).

DISTRIBUTION

A) Distribution Sites

Protein Binding

98% or more (Lennernas, 2003; Prod Info Lipitor(R), 2003)

B) Distribution Kinetics

Volume of Distribution

381 liters(Lennernas, 2003).

Following a 5-milligram intravenous infusion, the volume of distribution was 381 liters (Lennernas, 2003).

Metabolism

A) Metabolism sites and kinetics

1) LIVER, significant (Lennernas, 2003).

a Hepatic cytochrome P450 3A4 is the major metabolic pathway of atorvastatin (Lennernas, 2003).

b Atorvastatin is a candidate for drug-drug interactions when co-administered with potent CYP3A4 inhibitors, such as itraconazole, erythromycin, and grapefruit juice. Glucuronidation is another step in the metabolism of atorvastatin and its metabolites, and gemfibrozil is thought to inhibit glucuronidation of atorvastatin (Lennernas, 2003).

EXCRETION

A) Kidney

Renal Excretion (%)- 1 to 2

B) Other

BILE

Atorvastatin and its metabolites are eliminated mostly in the bile; the biliary route is the major route of elimination of atorvastatin and its metabolites (Lennernas, 2003; Prod Info Lipitor(R), 2003).

Elimination Half-life

A) Parent compound

- 7 to 14 hours (Lennernas, 2003; Prod Info Lipitor(R), 2003; Gibson et al, 1996).
    - Half-life is longer in elderly (19 hours) than in young subjects (Gibson et al, 1996).
    - Average half-life was 11.5 and 11.8 hours, respectively, after single and multiple dosing of atorvastatin 40 milligrams in a

study of 23 patients on hemodialysis. Average half-life was 10.9 and 14.7 hours, respectively, after single and multiple dosing of atorvastatin 80 milligrams in the same study. There was high inter-subject variability (Lins et al, 2003).

B) Metabolites

9 to 32 hours (Lins et al, 2003)

a After a single dose of 40 milligrams (mg) atorvastatin, the half-life of o-OH- atorvastatin ranged between 8.7 and 10.8 hours in healthy volunteers. The half-life was 23.6 and 32.1 hours after multiple dosing of 40 mg and 80 mg, respectively, in healthy volunteers (Lins et al, 2003).

b The half-life of o-OH-atorvastatin 18 and 22.3 hours after single and multiple dosing of atorvastatin 40 milligrams in a study of 23 patients on hemodialysis. Average half-life was 17.7 and 19 hours, respectively, after single and multiple dosing of atorvastatin 80 milligrams in the same study. There was high inter-subject variability (Lins et al, 2003).

CAUTIONS

Contraindications

- Hypersensitivity to atorvastatin
- Liver disease
- Pregnancy or lactation
- Unexplained, persistent elevation of serum transaminases

Precautions

a Concomitant therapy with fibrates, niacin, cyclosporine, erythromycin, or azole antifungals may increase the risk of myopathy

b Heavy alcohol use

c History of liver disease

d Reduce doses or discontinue therapy if serum transaminase levels 3 times the upper limit of normal persist

e Withhold temporarily or discontinue therapy in any patient who develops a condition suggestive of or predisposing to myopathy or renal failure

POLYMER PROFILE

EUDRAGIT RS100:

- Ammonio Methacrylate Copolymer, Type A“ Ph. Eur.
- Ammonio Methacrylate Copolymer, Type A " USP/NF
- Aminoalkylmethacrylate Copolymer RS" JPE

Chemical structure

EUDRAGIT® RS 100 is copolymer of acrylic and methacrylic acid esters with a low content in quaternary ammonium groups. The ammonium groups are present as salts and make the polymers permeable.

The average molecular weight is approx. 150,000.

Characteristics

Description

EUDRAGIT® RS 100: colourless, clear to cloudy granules with a faint amine-like odour.

Solubility

1 g of the substances dissolves in 7 g aqueous methanol, ethanol and isopropyl alcohol (containing approx. 3 % water), as well as in acetone, ethyl acetate and methylene chloride to give clear to cloudy solutions. The substances are practically insoluble in petroleum ether, 1 N sodium hydroxide and water.

Tests

Test solution

A 12.5 % solution of the dry substance is used for the test solution: a quantity of the substance of corresponding to 12.5 g dry substance is dissolved in a mixture of 60 % (w/w) isopropyl alcohol and 40 % (w/w) acetone.

Particle size

EUDRAGIT® RS: at least 90 % < 0.315 mm according to Ph. Eur. 2.1.4 or USP <811>.

Film formation

When the Test solution is poured onto a glass plate a clear film forms upon evaporation of the solvents.

Viscosity / Apparent viscosity

Max. 15 mPa. s. The viscosity of the Test solution is determined by means of a Brookfield viscometer (UL adapter / 30 rpm / 20 °C).

Refractive index

nD 20: 1.380 - 1.385. The refractive index of the Test solution is determined according to Ph. Eur. 2.2.6.

Relative density

d_{20} 20 : 0.816 - 0.836. The relative density of the Test solution is determined according to Ph. Eur. 2.2.5.

Monomers

Max. 100 ppm ethyl acrylate and max. 50 ppm methyl methacrylate according to the Ph. Eur. or USP/NF monograph.

IDENTITY TESTING

First identification

The material must comply with the tests for "Assay" and "Viscosity / Apparent viscosity."

Second identification

IR spectroscopy on a dry film approx. 15 µm thick. To obtain the film, a few drops of the Test solution are placed on a crystal disc (KBr, NaCl) and dried in vacuo for about 2 hours at 70 °C. The figures on page 4 show the characteristic bands of the ester groups at 1,150 - 1,190 and 1,240 - 1,270 cm-1, as well as the C = O ester vibration at 1,730 cm-1. In addition, CHX vibrations can be discerned at 1,385, 1,450, 1,475 and 2,950 - 3,000 cm-1.

Detection in dosage forms

The dosage forms are extracted using the solvents listed under "Solubility," if necessary after crushing. Insoluble substances are isolated by filtration or centrifugation. The clear filtrate is boiled down and the residue identified by IR spectroscopy.

Storage

- Protect from warm temperatures (USP, General Notices).
- Protect from moisture.

EUDRAGIT® RS 100 tend to form lumps at warm temperatures. This has no influence on the quality. The lumps are easily broken up again.

Incompatibilities

Incompatibilities occur with certain polymethacrylate dispersions depending upon the ionic and physical properties of the polymer and solvent. For example, soluble electrolytes, pH changes, some organic solvents, and extremes of temperature may cause coagulation; for example, dispersions of Eudragit L 30 D, RL 30D, L 100-55 and Rs 30 D are incompatible with magnesium stearate. Eastacryl 30D, Kollicoat MAE 30D, and Kollicoat MAE 30 DP are also incompatible with magnesium state.

Interactions between polymethacrylates and some drugs can occur, although solid polymethacrylates and organic solutions are generally more compatible than aqueous dispersions.

Safety

Polymethacrylate copolymers are widely usd as film- coating materials in oral pharmaceutical formulations. They are also used in topical formulations and are generally regarded as nontoxic and nonirritant materials.

A daily intake of 2 mg/kg body-weight of Eudragit (equivalent to approximately 150 mg for an average adult) may be regarded as essentially safe in humans.

Handling precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Additional measures should be tkane when handling organic solutions of polymethacrylates. Eye protection, gloves, and a dust mask or respirator are recommended. Polymethacrylates should be handled in well-ventilated environment and measures should be taken to prevent dust formation[63].

HYPROMELLOSE

Nonproprietary Names

BP: Hypromellose

JP: Hydroxypropylmethylcellulose

PhEur: Hypromellosum

USP: Hypromellose

Synonyms

Benecel MHPC; hydroxypropyl methyl ether; E464; hydroxypropyl methylcellulose; HPMC; Methocel; methylcellulose propylene glycol ether; merthyl hydroxypropylcellulose; Metolose ; Pharmacoat ; Spectracel 6 ; Spectracel 15; Tylopur.

Chemical Name and CAS registry number

Cellulose, 2-hydroxypropyl-methyl ether [9004-65-3]

Empirical formula molecular weight

The PhEur 2002 describes hypromellose as a partly O-methylated and O-(2-hydroxypropylated) cellulose. It is available in several grades that vary in viscosity and extent of substitution. Grades may be distinguished by appending a number indicative of the apparent viscosity, in mPa s, of a 2% w/w aqueous solution at 20℃. Hypromellose defined in the USP 25 specifies the substitution type by appending a four-digit number to the nonproprietary name: e.g., hypromellose 1828. The first two digits refer to the approximate percentage content of the methoxy group (OCH3). The second two digits refer to the approximate percentage content of the methoxy group (OCH3). The second two digits refer to the approximate percentage content of the hydroxypropoxy group (OCH2CH (OH) CH3), calculated on a dried basis. Molecular weight is approximately 10 000-1 500 000. The Jp 2001 includes three separate monographs for

hypromellose: hydroxypropylmethylcellulose 2208, 2906, and 2910, respectively.

Functional category

Coating agent; film-former; rate – controlling polymer for sustained release; stabilizing agent; suspending agent; tablet binder; viscosity – increasing agent.

Applications in pharmaceutical formulation or technology

Hypromellose is widely used in oral and topical pharmaceutions, Particularly ophthalmic preparations. Compared with methylcellulose, hypromellose produces solutions of greater clarity, with fewer undispersed fibers present, and is therefore preferred in formulations for ophthalmic use. Hypromellose at concentrations between 0.45-1.0% w/w may be added as a thickening agent to vehicles for eye drops and artificial tear solutions.

Hypromellose is also used as an emulsifier, suspending agent, and stabilizing agent in topical gels and ointments. As a protective colloid, it can prevent droplets and particles from coalescing or agglomerating, thus inhibiting the formation of sediments.

In addition, hypromellose is used in the manufacture of capsules, as an adhesive in plastic bandages, and as a wetting agent for hard contact lenses. It is also widely used in cosmetics and food products.

Description

Hypromellose is an odorless and tasteless, white or creamy white fibrous or granular powder.

Pharmacopeial specifications

Typical Properties

Acidity / alkalinity: pH = 5.5 – 8.0 for a 1% w/w aqueous solution

Ash: 1.5-3.0% depending upon the grade

Autoignition temperature: 360℃

Density (tapped): 0.557 g/cm^3

Density (tapped): 1.326 g/cm^3

Melting point: browns at 190-200℃; chars at 225-230℃.

Glass transition temperature is 170-180℃.

Moisture content: hypromellose absorbs moisture from the atmosphere, the amount of water absorbed depending and relative humidity of the surrounding air.

Solubility: soluble in cold water, forming a viscous colloidal solution; practically insoluble in chloroform, ethanol (95%), and ether, but soluble in mixtures of ethanol and dichloromethane, mixtures of methanol and dichloromethane, and mixtures of water and alcohol. Certain grades of hypromellose are soluble in aqueous acetone solutions, mixtures of dichloromethane and propan-2-ol, and other organic solvents.

Specific gravity: 1.26

Viscosity (dynamic): Wide ranges of viscosity types are commercially available. Aqueous solutions are most commonly prepared, although hypromellose may also be dissolved in aqueous alcohols such as ethanol and propan-2-ol provided the alcohol content is less than 50% w/w. Dichloromethane and ethanol mixtures may also be used to prepare viscous hypromellose solutions. Solutions prepared using organic solvents tend to

be more viscous; increasing concentration also produces more viscous solutions;

Methocel grade	Nominal	Viscosity (MPa s)
K 100LVP	100	80-120
K4M	4000	3000-5600
K15MP	15000	12000-2100
K100MP	100 000	80 000-120 000

To prepare an aqueous solution, it is recommended that hypromellose is dispersed and thoroughly hydrated in about 20-30% of the required amount of water. The water should be vigorously stirred and heated to 80-90℃, then the remaining hypromellose added. Cold water should then be added to produce the required volume.

When a water – miscible organic solvent such as ethanol, glycol, or mixtures of ethanol and dichloromethane is used, the hypromellose should first be dispersed into the organic solvent, at a ratio of 5-8 parts of solvent to part of hypromellose. Cold water is then added to produce the required volume.

Stability and storage conditions

Hypromellose powder is a stable material, although it is hygroscopic after drying.

Solutions are stable at pH 3-11. Increasing temperature reduces the viscosity of solutions. Hypromellose undergoes a reversible sol-gel transformation upon heating and cooling, respectively. The gel point is 80-90℃, depending upon the grade and concentration of material.

Aqueous solutions are comparatively enzyme-resistant, providing good viscosity stability during long-term storage.However, aqueous solutions are liable to microbial spoilage and should be preserved with an

antimicrobial preservative: when hypromellose is used as a viscosity – increasing agent in ophthalmic solutions, benzalkonium chloride is commonly used as the preservative. Aqueous solutions may also be sterilized by autoclaving; the coagulated polymer must be redispersed on cooling by shaking.

Hypromellose powder should be stored in a well-closed container, in a cool, dry place.

Incompatibilities

Hypromellose is incompatible with some oxidizing agents. Since it is nonionic, hypromellose will not complex with metallic salts or ionic organics to form insoluble precipitates.

safety

Hypromellose is widely used as an excipient in oral and topical pharmaceutical formulations. It is also used extensively in cosmetics and food products.

Hypromellose is generally regarded as a nontoxic and nonirritant material, although excessive oral consumption may have a laxative effect. The WHO has not specified an acceptable daily intake fro hypromellose since the levels consumed were not considered to represent a hazard to health.

LD_{50} (mouse, IP): 5 g/kg (16)

LD_{50} (rat, IP): 5.2 g/kg

Handling precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Hypromellose dust may be irritant to the eyes and eye protection is recommended. Excessive dust generation should be avoided to minimize the risks of explosion. Hypromellose is combustible[63].

ETHYLCELLULOSE

Nonproprietary Names

BP: Ethylcellulose

PhEur: Ethylcellulosum

USPNF: Ethylcellulose

Synonyms

Aquacoat ECD; Aqualon; E462; Ethocel; Surelease.

Chemical Name and CAS registry number

Cellulose ethyl ether [9004-57-3]

Empirical formula & molecular weight

Ethylcellulose with complete substitution (DS=3) is $C_{12}H_{23}O_6$ $(C_{12}H_{22}O_5)_n$ $C_{12}H_{23}O_5$ where n can vary to provide a wide variety of molecular weights. Ethylcellulose, and ethyl ether of cellulose, is a long-chain polymer of β– anhydroglucose units jointed together by acetal linkages.

Functional category

Coating agent; flavoring fixative; tablet binder; tablet filler; viscosity – increasing

Applications in pharmaceutical formulation or technology

Ethylcellulose is widely used in oral and topical pharmaceutical formulations; see Table A.

The main use of ethylcellulose in oral formulations is as a hyudrophobic coating agent for tablets and granules. Ethylcellulose coatings are used to modify the release to a drug to mask an unpleasant taste, or to improve the stability of a fomualtion; for example, where granules are coated with ethylcellulose to inhibit oxidation. Modified – release tablet formulations may also be produced using ethylcellulose as a matrix former.

Ethylcellulose, dissolved in an organic solvent or solvent mixture, can be used on its own to produce water – insoluble films. Higher – viscosity ethylcellulose grades tend to produce stronger and more durable films. Ethylcellulose films may be modified to alter their solubility by the addition of hypromellose or a plasticize. An aqueous polymer dispersion (or latex) of ethylcellulose such as Aquacoat ECD (FMC Biopolymer) or Surelease (Colorcon) may also be used to produce ethylcellulose films without the need for organic solvents.

Drug release through ethylcellulose – coated dosage forms can be controlled by diffusion through the film coating. This can be a slow process unless a large surface area (e.g.pellets or granules compared with tablets) is utilized. In those instances, aqueous ethylcellulose dispersions are generally used to coat granules or pellets. Ethylcellulose-coated beads and granules have also demonstrated the ability to absorb pressure and hence protect the coating from fracture during compression.

High-viscosity grades of ethylcellulose are used in drug microencapsulation.

Release of a drug from an ethylcellulose microcapsule is a function of the microcapsule wall thickness and surface area.

In tablet formulations, ethylcellulose may additionally be employed as a binder; the ethylcellulose may additionally be wet-granulated with a solvent such as ethanol (95%). Ethylcellulose produces hard tablets with low friability, although they may demonstrate poor dissolution.

Ethylcellulose has also been used as an agent for delivering therapeutic agents from oral (e.g., dental) appliances.

In topical formulations, Ethylcellulose is used as a thickening agent in creams, lotions, or gels, provided an appropriate solvent is used.

Ethylcellulose is additionally used in cosmetics and food products.

Table: A- Uses of Ethylcellulose

Use	Concentration (%)
Microencapsulation	10.0-20.0
Sustained – release tablet coating	3.0-20.0
Tablet coating	1.0-3.0
Tablet granulation	1.0-30.0

Description

Ethylcellulose is a tasteless, free- flowing, white or light tan-colored powder.

Typical properties

Density (bulk): 0.4g/cm ^{3}

Glass transition temperature: 129-133℃

Moisture content:

Ethylcellulose absorbs very little water from humid air or during immersion, and that small amount evaporates readily.

Solubility

Ethylcellulose is practically insoluble in glycerin, propylene glycol, and water. Ethylcellulose that contains less than 46.5% of ethoxyl groups is freely soluble in chloroform, methyl acetate, and tetrahydrofuran, and in mixtures of aromatic hydrocarbons with ethanol (95%). Ethylcellulose that contains not less than 46.5% of ethoxyl acetate, methanol, and toluene.

Specific gravity: 1.12-1.15 g/cm^3

Viscosity

The viscosity of ethylcellulose is measured typically at 25 C using 5% w/v ethylcellulose dissolved in a solvent blend of 80% toluene: 20% ethanol (w/w). Grades of ethylcellulose with various viscosities are commercially available; see Table III. They may be used to produce 5% w/v solutions in organic solvent blends with viscosities nominally ranging from 7 to 100 mPas (7-100 cp). Specific ethylcellulose grades, or blends of different grades, may be used to obtain solutions of a desired viscosity. Solutions of higher viscosity tend to be composed of longer polymer chains and produce strong and durable films.

The viscosity of an ethylcellulose solution increase with an increase in ethylcellulose concentration; e.g., the viscosity of a 5% w/v solution of Ethocel Standard 4 Premium is 4mPas (4cP) and of a 25% w/v solution of

the same ethylcellulose grade is 850 mPas (850cP). Solutions with a lower viscosity may be obtained by incorporating a higher percentage (30-40%) of a low molecular –weight aliphatic alcohol such as ethanol, butanol, propan -2-ol, or n-butanol with toluene. The viscosity of such solutions depends almost entirely on the alcohol content and is independent of toluene.

In addition, nonpharmaceutical grades of ethylcellulose that differ in their ethoxyl content and degree of polymerization are available.

Stability and storage conditions

Ethylcellulose is a stable, slightly hygroscopic material. It is chemically resistant to alkalis, both dilute and concentrated, and to salt solutions, although it is more sensitive to acidic materials than are cellulose esters.

Ethylcellulose is subject to oxidative degradation in the presence of sunlight or UV light at elevated temperatures. This may be prevented by the use of antioxidant and chemical additives that absorb light in the 230-340 nm range.

Ethylcellulose should be stored at a temperature not exceeding 32℃ (90℉) in a dry area away from all sources of heat. It should not be stored next to peroxides or other oxidizing agents.

Incompatibilities

Incompatible with paraffin wax and microcrystalline wax.

Safety

Ethylcellulose is widely used in oral and topical pharmaceutical formulations. It is also used in food products. Ethylcellulose is not metabolized following oral consumption and is therefore a noncalorific

substance. Because ethycellulose is not metabolized it is not recommended for pareteral products; paranteral use may be harmful to the kidneys.

Ethylcellulose is generally regarded to be a health hazard; the WHO has not specified an acceptable daily intake.

LD50 (rabbit, skin): >5 g/kg (28)

LD50 (rat,oral): >5 g/kg

Handling precautions

It is important to prevent fine dust clouds of ethylcellulose from reaching potentially explosive levels in the air. Ethylcellulose is combustible. Ethylcellulose powder may be an irritant to the eyes and eye protection should be worn[63].

Nagaraj[64] *et.al.,***(2007)** developed simultaneous Quantitative resolution of Atorvastin calcium and Fenofibrate in pharmaceutical preparation by using derivative ratio spectrophotometry and chemometric Calibrations. The calibration was constructed by using the absorption data matrix corresponding to the concentration data matrix, with measurements in the range of 231-310nm (Δ λ=1nm) I their zero-order spectra. The Linearity range was found to be 4-22 and 2-20 mg/ml for Atorvastatin and Fenofibrate, respectively.

Udhumansha Ubaidulla[65] *et.al.,***(2007)** have developed the carvedilol transdermal patches which have great utility and are a viable option for effective and controlled management of hypertension. It was developed with different ratios of hydrophilic and hydrophobic polymeric combinations by the solvent evaporation techniques. The results followed Higuchi Kinetics (r=0.9953- 0.9979), and the mechanism of release was diffusion mediated. As a result, patches with Eudragit RL: Eudragit RS (at 8:2) and Ethyl cellulose: polyvinylpyrrolidone. (at 7.5:2.5) combinations were chosen for further *in vivo* studies. The antihypertensive activity of the patches in comparison with that of oral carvedilol was studied using methylprednisolone acetate- induced hypertensive rats. It was observed that both the patches significantly controlled hypertension from the first hour with improved bioavailability of 62% and 71% respectively. The developed transdermal patches increase the efficacy of carvedilol for the therapy of hypertension.

Tanwar Y.S[66] *et.al.,***(2007)** developed transdermal patches of carvedilol with a HPMC- drug reservoir by the solvent evaporation technique. In this investigation, the membranes of Eudragit RL100 and

Eudragit RS100 were cast to achieve controlled release of the drug. The prepared patches possessed satisfactory physicochemical characteristics. Thickness, mass and drug content were uniform in prepared patches. Moisture vapour transmission through the patches followed zero-order kinetics. In vitro permeation studies were performed using K-C diffusion cell across hairless guinea pig skin and followed the super case II transport mechanism. The effects of non-ionic surfactants Tween 80 and span 80 on drug permeation were studied. The non-ionic surfactants in the patches increased the permeation rate, span 80 exhibiting better enhancement relative to Tween 80. The patches were seemingly free of potentially hazardous skin irritation.

Reddy M.S. [67] *et.al.,***(2006)** developed transdermal patches of metoclopramide hydrochloride using polyvinyl alcohol and polyvinyl pyrrolidone for the treatment of vomiting and nausea. The physicochemical parameters like thickness, drug content, weight variation, moisture content, moisture uptake and drug permeation studies (through dialysis sac and rat skin) were evaluated for the prepared patches. The formulations exhibited uniform thickness and weight, good drug content and little moisture content and uptake. In the in vitro drug permeation studies, the formulations showed burst release of the drug in initial hours and thereafter drug was released slowly up to 12 hrs. The drug release mechanism from the patches was found to be diffusion dominated. The stability studies indicated that all patches maintained good physical appearance and drug content for 6 months at 40° / 75% RH.

Patel Parul[68] *et.al.,***(2006)** prepared monolithic transdermal films of repaglinide using Eudragit NE 30D, Acrycoat RL100, Cellulose acetate, Polyvinyl Pyrrolidone, Ethylcellulose (individual and combination). Those prepared films were evaluated for weight variation, thickness uniformity,

tensile strength, content uniformity and invitro permeation study. The order of permeation of the drug from different polymeric films Eudragit NE30D > Ethylcellulose: Polyvinyl Pyrrolidone > Cellulose acetate: PVP> Ethylcellulose > Eudragit RL100: PVP > cellulose acetate > Acrycoat: PVP. The drug release mechanism from all monolithic systems was diffusion controlled and followed zero order kinetics.

Rathore RPS[69] *et.al.,***(2006)** fabricated matrix type transdermal patches of Terbutaline sulphate using polymers like ethylcellulose (EC), Povidone (PVP) and cellulose acetate (CA). The formulated patches were found to be physically stable with regard to drug content, tensile strength, folding endurance, thickness and weight variation. Formulations CP3 (CA: PVP at 3:2) and EP2 (EC: PVP at 2:3) were found to be best suitable and found to follow diffusion controlled permeation.

Saraf Swarnlata[70] *et.al.,* developed both reservoir as well as matrix transdermal delivery system of timolol maleate using polymers like hydroxypropyl methyl cellulose, Ethylcellulose, and polyvinyl alcohol. Out of all the formulations PVA_{10} (i.e. PVA 10% w/v) and HE_2 (HPMC: EC: : 2:8) were found to be physically stable regarding drug content, tensile strength, toughness and water vapour transmission rate. Both the patches follows diffusion controlled drug permeation and high permeation with PVA_{10} while reservoir system follows zero order permeation kinetics.

Rajagopal k.[71] *et.al.,***(2005)** formulated the matrix type transderamal patches of Nimesulide using different polymers; like HPMC, EC, and MC; alone or in combination ; dibutyl phthalate as the plasticizer and aluminum foil as the backing membrane. In-vitro release studies of the prepared formulations were performed by K-C diffusion cell through cellophane

membrane in phosphate buffer solution (pH 7.4). After all the evaluations, the studies showed that Hydroxy Propyl Methyl Cellulose (HPMC) and Ethyl Celluose (EC) Combination (2:2) might be the suitable polymer combination for development of transdermal drug delivery system of Nimesulide.

Biswajit Mukherjee[72] *et.al.,***(2005)** developed a matrix type transdermal drug delivery system of Dexamethasone using blends of two different polymeric combinations, Povidone(PVP) with ethyl cellulose(EC) and Eudragit with PVP. Physical studies including moisture content, moisture uptake, flatness to study the stability of the formulation. In vitro dissolution and diffusion studies were performed to study the drug content and diffusion profile of the patches, respectively. The formulations of PVP: EC (1:5) was found to provide slowest release of drug. Hence it was concluded that PVP- EC polymers are better suited than PVP- Eudragit polymers for the development of TDDS of Dexamethasone.

Ubaidulla[73] *et.al.,***(2004)** aimed at improving the permeability of Carvedilol from transdermal films, which is made by using hydroxy propyl methyl cellulose (HPMC) as polymeric matrix and propylene glycol as plasticizer. Sodium lauryl Sulphate (SLS), Tween 20, Dimethyl Sulfoxide (DMSO) and propylene glycol (PEG 400) were used as permeation enhancers. It was found that the permeation enhancers increased the permeation of carvedilol in the order as: Tween 20> SLS> PEG 400 > DMSO. The effect of iontophoresis on permeation of carvedilol transdermal films were studied alone and mixed with enhancers. The data clearly showed that permeation enhancers and iontophoresis synergistically enhanced permeability of carvedilol from its films. The results suggested that the combination of permeation enhancers and iontophoresis could be useful for increasing in the skin permeability of carvedilol through the

matrix TDDS.

Kusum Devi[74] *et.al.,***(2003)** designed and evaluated matrix diffusion controlled transdermal patches of verapamil hydrochloride using four different polymers (individual and combination): Eudragit RL100, Eudragit RS100, hydroxyl propyl methyl cellulose 15 cps, and ethyl cellulose. The effect of the polymers on the technological properties, i.e., drug releases, water vapour transmission rate (WVTR) and percentage moisture loss (ML), Percentage moisture absorption (MA), folding endurance, and thickness were evaluated. The patch containing ERL 100 alone showed maximum WVTR, % MA, and % ML, which could be attributed to its hydrophilic nature. As expected, substitution with ER100, HPMC, and EC decreased all the above values in accordance with their decreasing degree of hydrophilicity. Among the eight formulations, Eudragit RL100: HPMC (8:2) combination emerged as the most satisfactory formulation insofar as its technological properties were concerned out in rabbits. The pharmacokinetic parameters calculated from blood levels of the drug revealed a profile typical of a sustained release formulation.

Biswajit Mukherjee[75] *et.al.,***(2003)** aimed at selecting a suitable formulation for the development of transdermal drug- delivery system of diltiazem hydrochloride. Transdermal patches of the drug, employing different ratios of polymers, ethylcellulose (EC); and Povidone (PVP) were developed and evaluated for the potential drug delivery using depilated freshly excised abdominal mouse skin. The influence of different film compositions on in vitro drug permeation into receptor fluid were studied using a modified Franz diffusion cell. The cumulative amount of drug was found to be proportional to the square root of time, i.e., Higuchi kinetics. From this study, it was concluded that the films compsed of Povidone: ethylcellulose (1:2) should be selected for the development of transdermal

drug-delivery system of diltiazem hydrochloride, using a suitable adhesive layer and backing membrane, for potential therapeutic use.

Gopal Rao, M.,[76] *et.al.,***(2001)** developed a matrix type transdermal drug delivery system of Propranolol hydrochloride using polymers like PVA and PVP alone and in combinations. Glycerol was used as the plasticizer and tween 80 was used as the permeation enhancer. Along with the physico-chemical evaluation and in vitro drug diffusion studies, the effect of formulation variables such as plasticizer concentration, film thickness, concentration of permeation enhancer, loading dose on weight variation, thickness, moisture content, drug content and in vitro drug release were studied. Due to the increase in PVP and plasticizer concentration, the moisture content got increased. Increase in loading dose, permeation enhancer and plasticizer concentration, synergistically improved the in vitro drug release from the formulated patches. Increasing the thickness significantly retarded the drug release. Accelerated stability studies indicated that the formulated patch had adequate shelf life. The primary skin irritation studies on animal and human volunteers revealed that formulated patches were compatible with skin. As the result formulation F_{13} PVA: PVP at 4: 1 was found to be an ideal patch.

Gopal Rao, M.,[77] *et.al.,***(2001)** developed a matrix type transdermal drug delivery system of verapamil hydrochloride using polymers like cellulose acetate butyrate (CAB) and polyvinyl pyrrolidone (PVP) alone and in combinations. Dibutyl phthalate was used as the plasticizer and Isopropyl myristate was used as the permeation enhancer. Along with the physico-chemical evaluation and in vitro drug diffusion studies, the effect of formulation variables such as plasticizer concentration, film thickness, concentration of permeation enhancer, loading dose on weight variation, thickness, moisture content, drug content and in vitro drug release were

studied. Due to the increase in PVP and plasticizer concentration, the moisture content got increased. Increase in loading dose, permeation enhancer and plasticizer concentration, synergistically improved the in vitro drug release from the formulated patches. Increasing the thickness significantly retarded the drug release. Accelerated stability studies indicated that the formulated patch had adequate shelf life. The primary skin irritation studies on animal and human volunteers revealed that formulated patches were compatible with skin. As the result formulation F_{13} CAB: PVP at 4: 1 was found to be an ideal patch.

Gopal Rao, M.,[78] *et.al.,***(2000)** developed a matrix type transdermal drug delivery system of Metoprolol tartrate using polymers like PVA and PVP alone and in combinations. Glycerol was used as the plasticizer and tween 80 was used as the permeation enhancer. Along with the physico-chemical evaluation and in vitro drug diffusion studies, the effect of formulation variables such as plasticizer concentration, film thickness, concentration of permeation enhancer, loading dose on weight variation, thickness, moisture content, drug content and in vitro drug release were studied. Due to the increase in PVP and plasticizer concentration, the moisture content got increased. Increase in loading dose, permeation enhancer and plasticizer concentration, synergistically improved the in vitro drug release from the formulated patches. Increasing the thickness significantly retarded the drug release. As the result formulation N_2 PVA: PVP at 2:1 with 10% glycerol and thickness of 172.73± 4.17 microns and loaded dose 4mg/ cm^2 was found to be an ideal patch.

Gopal Rao, M.,[79] *et.al.,***(2000)** developed a matrix type transdermal drug delivery system of Isosorbide dinitrate using polymers like cellulose acetate butyrate (CAB) and polyvinyl pyrrolidone (PVP) alone and in combinations. Dibutyl phthalate was used as the plasticizer and isopropyl

myristate was used as the permeation enhancer. Along with the physico-chemical evaluation and in vitro drug diffusion studies, the effect of formulation variables such as plasticizer concentration, film thickness, concentration of permeation enhancer, loading dose on weight variation, thickness, moisture content, drug content and in vitro drug release were studied. Due to the increase in PVP and plasticizer concentration, the moisture content got increased. Increase in loading dose, permeation enhancer and plasticizer concentration, synergistically improved the in vitro drug release from the formulated patches. Increasing the thickness significantly retarded the drug release. Accelerated stability studies indicated that the formulated patch had adequate shelf life. The primary skin irritation studies on animal and human volunteers revealed that formulated patches were compatible with skin. As the result formulation F_{13} CAB: PVP at 4: 1 was found to be an ideal patch.

Xu DH.[92] *et.al.,***(1999)** studied the synergistic effects of ethosomes and chemical enhancers on enhancement of naloxone permeation through human skin**.** The purpose of this study was to investigate the effects of ethosomes, chemical enhancers and their binary combination on the in vitro permeability enhancement of naloxone through human skin. Franz diffusion cells were used for the percutaneous absorption studies. Propylene glycol (PG), N, N-dimethyl formamide (N, N-DMF), N, N-dimethyl acetamide (N, N-DMA), dimethyl sulfoxide (DMSO), Azone and polyethylene glycol 400 (PEG400), were chosen as the chemical enhancers. Naloxone ethosomes showed 11.68 times increase in steady-state flux compared to phosphate buffered solution (PBS). Ethosomes in combination with chemical enhancers synergistically increased ($p < 0.05$) in vitro flux of naloxone. Azone 3% + PG7% pretreated in ethosomal form dramatically enhanced the skin permeation of naloxone in vitro compared with ethosomes (steady-

state flux: 96.75 +/- 5.70 microg x cm (-2) x h (-1) vs 20.56 +/- 1.67 microg x cm (-2) x h(-1)). Ethosomal carrier and enhancers accumulated in the skin after 24 h were greater than that of PBS.

OBJECTIVE OF THE PROJECT

Transdermal drug delivery system has been in existence for a long time. The occurrence of systemic side effects with some of these formulations is indicative of absorption through skin. A number of drugs have been applied to the skin for systemic treatment. In a broad sense, the term transdermal delivery system includes all topically administered drug formulations intended to deliver the active ingredient into the general circulation. The advantages of transdermal drug delivery include its ease of use, patient compliance, sustained drug delivery, local application and safety. Oral medications must pass through the gastrointestinal tract, into the liver- where drugs are broken down, possibly lowering their effectiveness. With the transdermal patch, drugs enter directly into the bloodstream, reducing the risk of gastrointestinal side effects and bypassing breakdown by the liver.

In particular the invention relates to the methods and compositions for treating patients in need of statin therapy, for example for hyperlipidemia and hypercholestorlemia syndrome, including but not limited to those associated with diabetic conditions. Statin drugs also may affect the risk of clot formation and therefore risk of heart attack. These drugs also can lower LDL and contribute to lowering triglyceride-rich lipoprotein levels. The methods of embodiments of this invention are designed to produce a reduction or elimination of the side effects which commonly occur with statin drugs and to permit treatment of patients who cannot or do not wish to begin or continue statin therapy due to concomitant drug therapies, potential side effects, etc.

One such drug is atorvastatin calcium[62], which is a synthetic lipid-lowering agent and its molecular weight is 1209.42. Atorvastatin is rapidly

absorbed after oral administration and maximum plasma concentrations occur within 1 to 2 hours but the absolute bioavailability is approximately 14% and the systemic availability of HMG-CoA reductase inhibitory activity is approximately 30%. The low systemic availability is attributed to pre-systemic clearance in gastrointestinal mucosa and/or hepatic first-pass metabolism. So the objective becomes focused that formulating atorvastatin as transdermal patches improves its systemic availability as well ability to consistently administer the drug at a zero order rate and the availability to remove the drug rapidly from the user in cases of adverse effects, toxicity, or any other undesirable effects. An additional advantage is increase in patient compliance. Controlled release and efficient bioavailability through transdermal patches may results with lowering the dose required per day.

MATERIALS AND EQUIPMENTS USED

MATERIALS USED:

Table: 2

S.no	Materials	Grade	Source
01	Atorvastatin Calcium		Gift sample from Blue Cross Laboratories Limited.
02	Hydroxy Propyl Methyl Cellulose	E50 LV premium	Loba Chemie Pvt. Ltd.
03	Ethyl Cellulose	18-22 cp	Loba Chemie Pvt. Ltd.
04	Eudragit	RS100	Rohm Pharma
05	Glycerine	AR	S.d fine chemicals
06	Dimethyl Sulfoxide	AR	Merck Ltd
07	Dimethyl Formamide	AR	Hi-Pure fine Chem. Ind.
08	Chloroform	AR	Qualigens Fine Chemicals
09	Methanol	AR	Qualigens Fine Chemicals
10	Mercury		S.d fine chemicals
11	Calcium chloride	Anhydrous	Qualigens Fine Chemicals
12	Potassium di hydrogen phosphate	AR	Qualigens Fine Chemicals
13	Sodium hydroxide	AR	Qualigens Fine Chemicals
14	Sodium chloride	AR	Qualigens Fine Chemicals
15	TLC plates		Merck Ltd.
16	Potassium bromide	AR	Qualigens Fine Chemicals
17	Benzene	AR	Qualigens Fine Chemicals
18	Acetic acid	AR	Qualigens Fine Chemicals
19	Cellophane membrane	0.2µm	Sartorius Ltd.

EQUIPMENTS USED

Table: 3

S.NO	EQUIPMENT	MODEL/COMPANY
01	Franz Diffusion Cell	Fabricated one
02	UV Visible Spectrophotometer	Shimadzu UV- 1700
03	FT/ IR Spectrometer	FT/ IR JASCO-410
04	Digital balance	Shimadzu Electronic Balance
05	Hot air oven	Inlab Equipments
06	Magnetic stirrer	Remi Equipments
07	Circular mould dishes	Fabricated one
08	Laboratory stirrer with variable speed control	Remi Motors
09	Vacuum dessicator	-
10	Dial caliper	Aerospace Electronic Digital Micrometer
11	Single pan balance	Dhona 200 D

METHODOLOGY

PREFORMULATION STUDIES

Before the formulation of a drug substance into a dosage form, it is essential that it should be chemically and physically characterized. Pre-formulation studies give the information needed to define the nature of the drug substance and provide a framework for the drug combination with pharmaceutical excipients in the fabrication of a dosage form.

In the present work, pre- formulation studies on the compatibility between drug and polymer were carried out using thin layer chromatography and Infra- Red spectroscopy.

THIN LAYER CHROMATOGRAPHY:

A thin layer chromatography was carried out to study the interaction between the drug and polymers. For this the pure drug and its combinations with the polymers were subjected to chromatographic studies.

The following TLC system was used-

Precoated TLC plates:		Mfg by S.d fine chemicals
Adsorbant Layer	:	Silica gel G
Layer Thickness	:	200µm
Separation Technique:		Ascending
Size	:	10x 20 cm
Mobile phase	:	Chloroform:Benzene: Methanol:Aceticacid 6 : 3 : 1 : 0.1
Preparation of sample:		a suitable amount of pure drug or equivalent amount of the samples were dissolved in chloroform: methanol (1:1) and were used for spotting.

Amount applied : 10 µL

Detection : UV chamber.

The Rf values are given in the table: 5 and figure: 5.

FT/ IR spectral studies:

Compatibility studies of the drug and the polymers were carried out using FT/ IR JASCO-410 spectrometer. 1 part of the sample is mixed thoroughly with 3 parts of dried potassium bromide and it was compressed into transparent, thin pellets. The pellets are then scanned under IR region and the spectra were recorded and discussed in the later part.

PREPARATION OF STANDARD GRAPH OF ATORVASTATIN CALCIUM:

STANDARD STOCK SOLUTION

The stock solution (1mg/ml) of Atorvastatin calcium was prepared in methanol[68].

SCANNING OF ATORVASTATIN CALCIUM:

The above-prepared standard stock solution was scanned under UV region between 200- 400nm and 241 nm is found to be the absorption maxima wavelength and the same was used for further analysis.

STANDARD PLOT

With reference to **Nagraj[64]** *et.al.,* who found the linearity of Atorvastatin calcium as 4-22 mcg/ml a series of dilutions were prepared from the standard stock solution using phosphate buffer pH 7.4. The dilutions were made in such a way to obtain 4, 8, 12, 16, 20 mcg/ml concentration finally, using phosphate buffer pH 7.4. The absorbances were measure against the reagent blank using SHIMADZU UV 1700 spectrophotometer at 241nm (table: 10& figure: 13). Calibration graph was plotted against respective drug concentration versus absorbances at 241 nm.

GENERAL METHOD OF PREPARATION OF TRANSDERMAL PATCHES:

In the present study, matrix type transdermal patches of Atorvastatin calcium were prepared by moulding techniques. A flat circular glass moulds having diameter 4.5 cm and height of 1 cm with a total surface area of 15.91cm^2 was fabricated for this purpose.

A) PREPARATION OF CASTING SOLUTIONS:

The casting solutions were prepared by dissolving weighed quantities of polymers in a solvent mixture of chloroform and methanol at 1:1 ratio. The drug, plasticizer and permeation enhancers were then added to the various polymer solutions individually and thoroughly mixed to from a homogenous mixture (table: 4). It was placed aside without any disturbances to allow the entrapped air to bubble out.

B) PREPARATION OF TRANSDERMAL PATCHES:

About 3 ml of casting solutions were pipetted into circular glass moulds especially designed to hold contents, which is casted on mercury surface. The glass moulds containing the casting solutions were allowed for drying at room temperature for 24 hrs and the patches are dried in over at 40-45° for 30 minutes in order to remove the residual solvents. The patches were removed and cut into circular discs with 4.4cm diameter (15.21cm^2 surface area). These patches were wrapped in aluminum foil and stored in dessicator for further studies[65, 70, 72, 74].

Table: 4 COMPOSITIONS OF TRANSDERMAL PATCHES OF ATORVASTATIN CALCIUM

Ingredients	**T_1**	**T_2**	**T_3**	**T_4**	**T_5**	**T_6**	**T_7**	**T_8**	**T_9**	**T_{10}**	**T_{11}**	**T_{12}**	**T_{13}**	**T_{14}**	**T_{15}**	**T_{16}**	**T_{17}**	**T_{18}**	**T_{19}**	**T_{20}**	**T_{21}**
Atorvastatin Calcium in (mg)	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Hydroxyl Propyl Methyl Cellulose in Parts								45	4.0	3.5	3.0	2.5	2.0	1.0	4.5	4.0	3.5	3.0	2.5	2.0	1.0
Ethyl Cellulose in Parts	4.5	4.0	3.5	3.0	2.5	2.0	1.0	0.5	1.0	1.5	2.0	2.5	3.0	4.0							
Eudragit Rs.100 in Parts	0.5	1.0	1.5	2.0	2.5	3.0	4.0								0.5	1.0	1.5	2.0	2.5	3.0	2.0
Glycerol in % w/w	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30
DMSO in w/w	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20

T_1-T_7: 10%w/w of EC: ERS100 T_8-T_{14}: 5%w/w of HPMC: EC T_{15}-$T_{21:}$ 10%w/w of HPMC: ERS100

EVALUATION OF TRANSDERMAL PATCHES

The prepared patches were evaluated for their physico- chemical parameters, in vitro diffusion studies, skin irritation and stability studies[83].

PHYSICO- CHEMICAL PARAMETERS:

The matrices were evaluated for the following parameters[83, 84, 85, 86, 87, 88].

FILM THICKNESS:

The thickness was measured at six different places using an Electronic Digital Micrometer (AEROSPACE- CHINA) and the mean Value was calculated.

DETERMINATION OF AVERAGE WEIGHT AND WEIGHT VARIATION:

As weight variation between the formulated patches can lead to difference in drug content and in-vitro behaviour, a study was carried out by weighing 6 patches in an electronic balance (table: 6-8). The average weight of a patch and its standard deviation was calculated by using the following formulas.

Average weight of each patches = total weight of 5 patches/5

Standard deviation $= \sqrt{\frac{\sum (x-X)^2}{n-1}}$

Where x = weight of individual patch

X = average weight

n = number of patches

DETERMINATION OF TENSILE STRENGTH:

The instrument, which was designed in our laboratory, was used for the measurement of tensile strength. The strip was clamped at the static end and was attached to the movable rod on a railing with the help of a clip. The weights were gradually added to the pan to increase the pull force till the

film was cut. The elongation was determined simultaneously by noting the distance traveled by the pointer, before break of the film, on the graph paper. The weight required to break the film was noted as the break force (table: 6-8). The tensile strength was calculated using Allen's formula.

$$\text{TENSILE STRENGTH} = \frac{\text{BREAK FORCE}}{a \times b} \times \frac{(1 + \Delta L)}{L}$$

Figure 18: Tensile strength apparatus

DETERMINATION OF HARDNESS:

The apparatus designed in our laboratory to study the hardness of the strips consists of a wooden stand of 11cms height and top area of 16 X 16 cm. A small pan was fixed horizontally on one end of the 2 mm thick iron rod whose other end is reduced to sharp point. A hole of 0.2 cm diameter was made at the center of the top area of wooden stand for supporting the pan rod. An electric circuit was made through a 3-volt battery in such a way that the bulb lights up only when circuit is completed through the contact of the metal plate and the sharp end of the rod. The film was placed between the metal plate and the sharp end of the rod. The weights were gradually added to the pan, at an interval of 10 seconds for the stabilization of force

till the bulb was glown. The final weight was considered as the measure of hardness (table: 9).

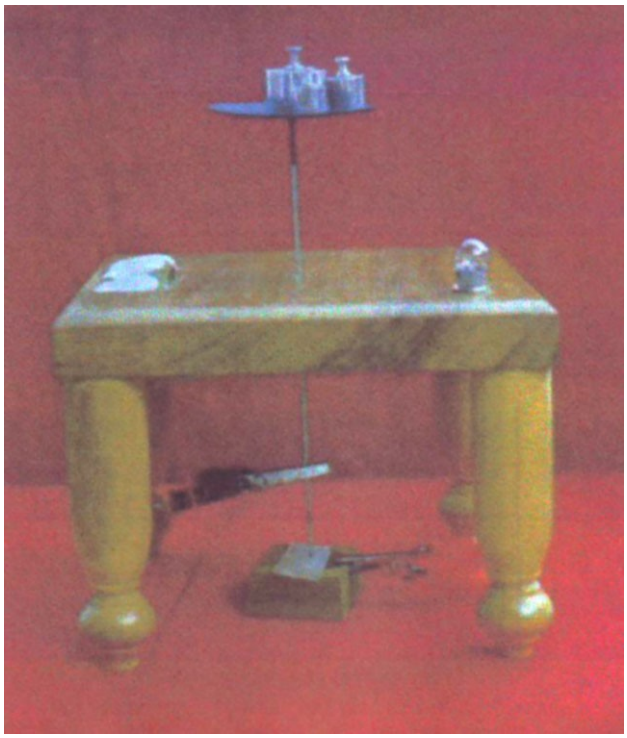


Figure 18: Hardness apparatus for transdermal patches

DETERMINATION OF PERCENTAGE MOISTURE CONTENT:

Moisture content can influence the mechanical strength and drug release behaviour of the transdermal therapeutic systems and therefore, in the present study determination of the moisture of the formulated patch was estimated by keeping the patch under vacuum desiccation until constant weights were obtained (table: 6-8). The percentage moisture content of the patch was calculated by the following formula.

$$\text{Percentage moisture content} = \frac{\text{Initial weight- Final weight}}{\text{Initial weight}}$$

DETERMINATION OF PERCENTAGE MOISTURE UPTAKE:

The weighed films kept in a desiccator at room temperature for 24hrs was taken out and exposed to 75% relative humidity (a saturated solution of sodium chloride) in a desiccator until a constant weight for the film was calculated as the difference between final and initial weight with respect to initial weight (table: 6-8).

$$\text{Percentage moisture uptake} = \frac{\text{final weight- initial weight}}{\text{final weight}}$$

DETERMINATION OF DRUG CONTENT:

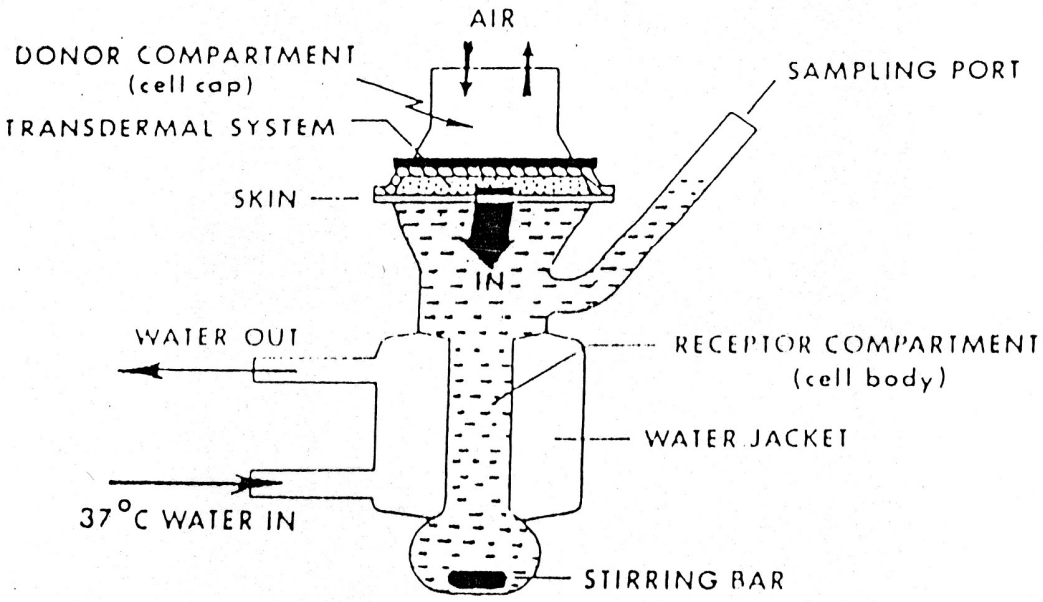
A formulated patch having 15.21cm^2 area was cut into small pieces and transferred into a graduated glass stoppered flask, which contained 100ml of mixture of chloroform and methanol in the ratio of 1:1, maintained at 45-50˚C. It was closed and shaked vigorously for 24 hours period in a shaker. The solution was filtered and the amount of drug present in the filterate was determined by using SHIMADZU UV-1700 spectrophotometer at 241nm. Similarly, blank solution was prepared using a dummy patch. The procedure was carried out in duplicate to determine the drug content. The following procedure was carried out induplicate to determine the drug content[89] (table: 6-8).

PROCEDURE FOR IN-VITRO DRUG RELEASE STUDIES:

In vitro permeation studies were performed by using Franz diffusion cell. It consists of a donor compartment and a receptor compartment. The cellulose membrane[84] was mounted between the donor compartment and receptor compartment of the diffusion cell. The formulated patches were placed over the membrane. The receptor compartment of the diffusion cell was filled with phosphate buffer PH 7.4. The whole assembly was fixed on a magnetic stirrer, and the solution in the receptor compartment was constantly and continuously stirred using magnetic bead at 50 rpm; the

temperature was maintained at 37±1^{0}C. The samples were withdrawn at different time intervals and analyzed for drug content. The receptor phase was replenished with an equal volume of phosphate buffer at each sample withdrawal. The cumulative percentage release of drug permeated per cm^2 of patches were plotted against time (table: 11-16& figure: 14-16).

Figure: 4 Franz Diffussion Cell



PRIMARY SKIN IRRITATION STUDIES

Patches were applied to the shaved skin on the backs of albino rats and secured using adhesive tape. On one side of the back, control patch and on other side an experimental patches were secured. The animals were observed for any sign of erythema or oedema for a period of 24 hours[65, 84].

STABILITY STUDIES

To any rational design and evaluation of dosage forms of drugs the stability of the active component must be a major criteria in determining their acceptance or rejection. Drugs instability by a change in the physical appearance color, odor, taste or texture of the formulation whereas in other instances chemical changes may occur which are not self-evident and may be ascertained through chemical analysis. Scientific data pertaining to the stability of a formulation leads to the prediction of the expected shelf life of the proposed product and when necessary to the reformulation of the dosage form.

Hence to assess the stability the selected films were kept at room temperature and at 40ºC over a period of 45 days. Patches were evaluated at 15^{th}, 30^{th}, 45^{th} day for their physico-chemical properties and in vitro diffusion studies.

RESULTS AND DISCUSSION

Transdermal drug delivery system of Atorvastatin calcium was developed using polymers like HPMC, EC, and ERS100; employing glycerine as plasticizer and DMSO as the permeation enhancer. Formulated 21 patches were subjected to physico- chemical evaluation such as physical appearance, weight variation, thickness, % moisture content, % moisture uptake, tensile strength, hardness and drug content. The in vitro drug release studies across cellulose membrane were conducted and the best formulations where subjected to stability studies.

COMPATIBILITY STUDIES

The compatibility studies confirmed that the absence of chemical interaction between the drug and polymers. The physico chemical parameters were evaluated.

Thin layer chromatography

TLC for the pure drug and in combination with the polymers were performed (fig:5) and the Rf values were reported in the table:5 The Rf values indicate the absence of chemical interaction between the drug and the polymers.

FT/ IR spectral studies

Compatibility studies of the drug and the polymers were carried using JASCO FT/ IR spectrometer and the spectras were given in the fig:6-12. The spectra obtained from the mixture of polymers and drug was found to be matching with the spectra of the pure drug. There was no appearance or disappearance of any characteristic peaks, which confirmed the absence of chemical interaction between the drug and polymer.

Thin layer chromatogram details

Figure:5

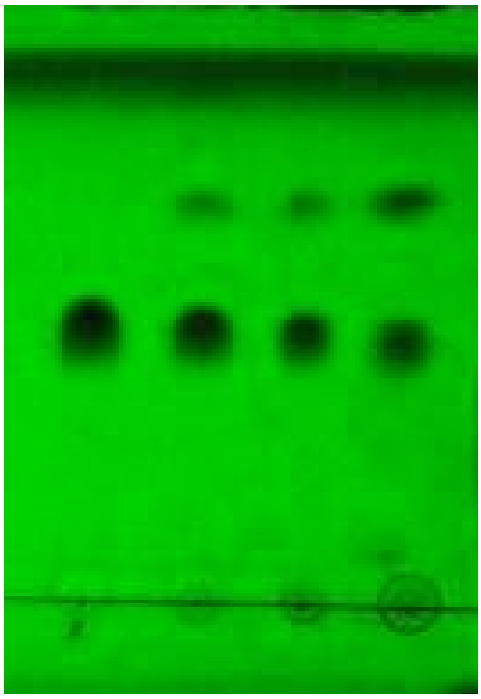
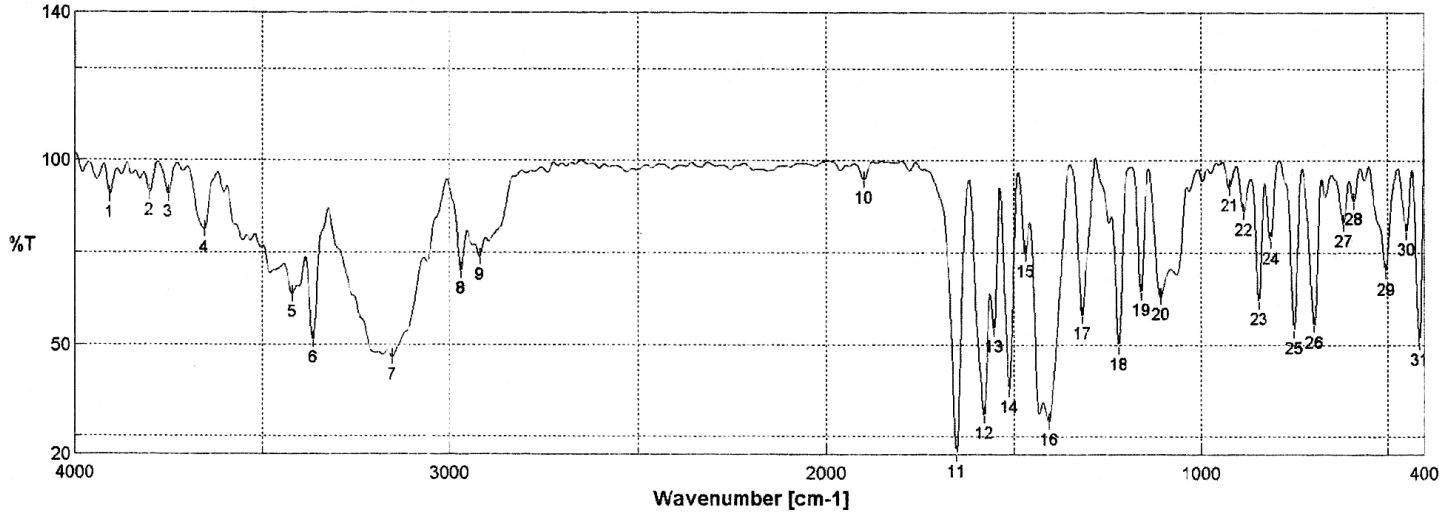


Table:5

S.NO	SAMPLE	Rf VALUE
1	Drug	0.48
2	Drug+ HPMC+ EC	0.47
3	Drug+ HPMC+ ERS100	0.47

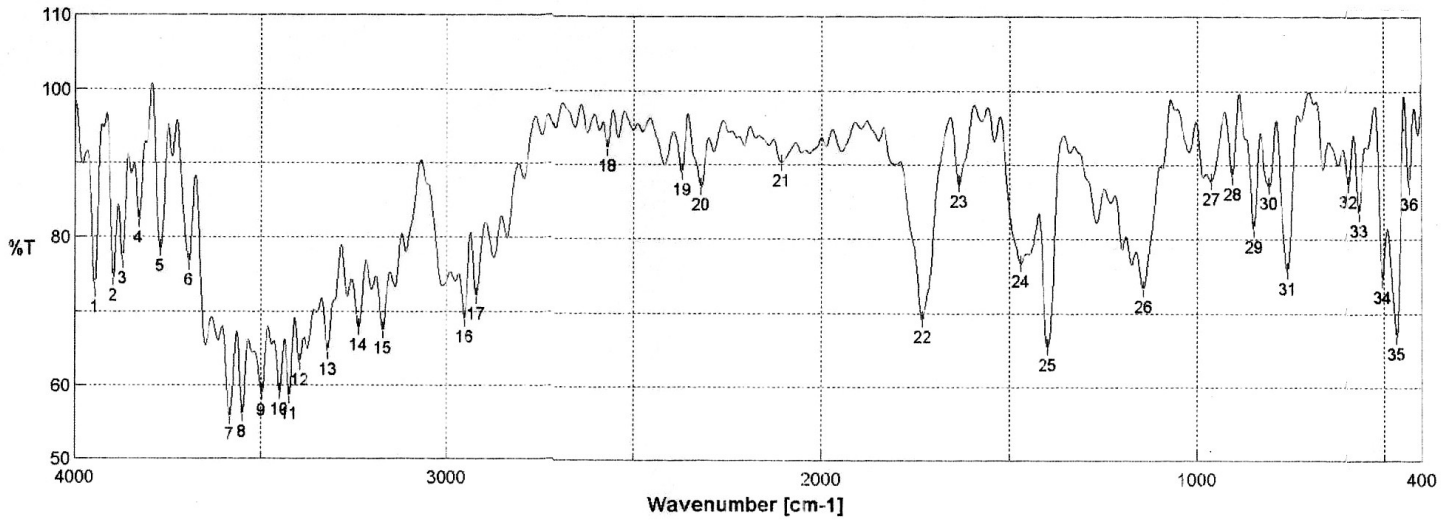
Figure: 6 IR Spectrum of Atorvastatin calcium



Accumulation	16	Resolution	4 cm-1
Zero Filling	ON	Apodization	Cosine
Gain	4	Scanning Speed	2 mm/sec
Date/Time	12/6/2007 11:07AM	Update	1/4/2008 4:15PM
Operator	C.Geetha		
File Name	Pure drug		
Sample Name	Pure drug		
Comment			

No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T
1	3904.18	90.5836	2	3800.04	91.2623	3	3751.83	90.7712	4	3657.34	81.1928	5	3419.17	63.6966
6	3366.14	51.2475	7	3155.94	46.5804	8	2969.84	70.0429	9	2921.63	73.9391	10	1901.47	94.8126
11	1650.77	20.399	12	1579.41	30.8466	13	1552.42	54.2983	14	1511.92	38.0736	15	1468.53	74.8431
16	1406.82	29.0883	17	1316.18	57.9198	18	1215.9	49.6048	19	1157.08	64.3819	20	1105.01	63.2327
21	922.771	92.7164	22	883.238	86.051	23	842.74	61.9004	24	809.956	78.414	25	746.317	53.9319
26	693.284	55.3926	27	617.109	82.9562	28	590.111	88.9129	29	504.294	69.892	30	449.333	80.8388
31	413.656	50.7881												

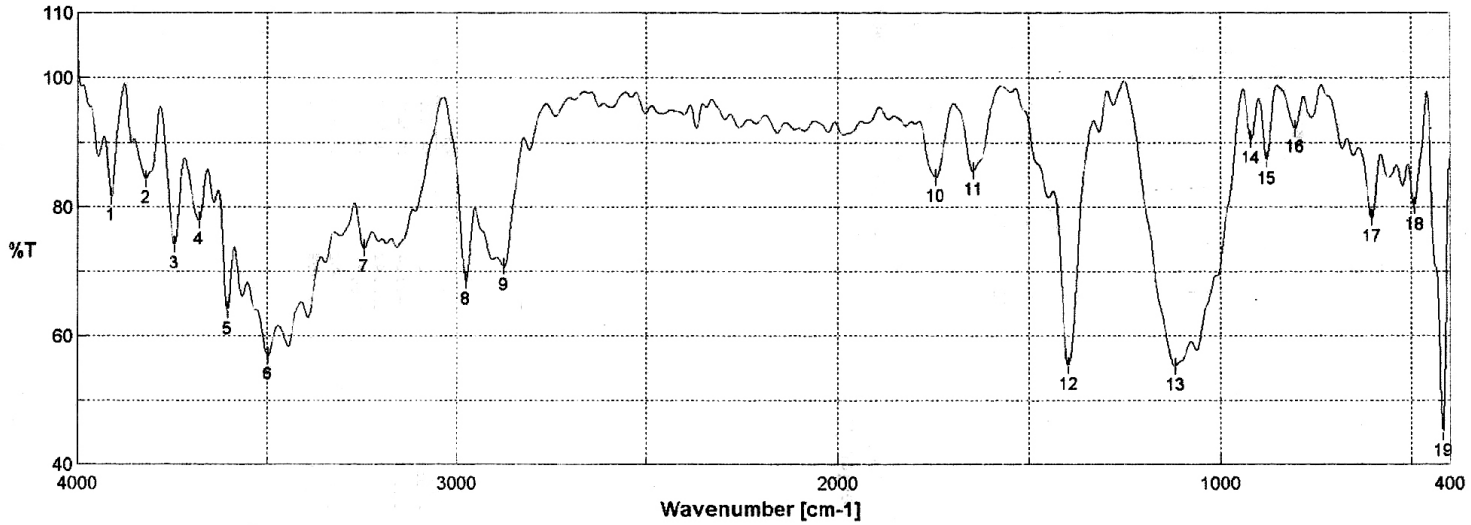
Figure: 7 IR Spectrum of ERS100



Accumulation	16	Resolution	4 cm-1
Zero Filling	ON	Apodization	Cosine
Gain	16	Scanning Speed	2 mm/sec
Date/Time	12/6/2007 11:24AM	Update	1/4/2008 4:05PM
Operator	C.Geetha		
File Name	ERS		
Sample Name	ERS		
Comment			

No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T
1	3945.64	72.9359	2	3895.5	74.5224	3	3870.43	76.7921	4	3825.11	82.3351	5	3767.26	78.5495
6	3693.01	76.6299	7	3585.02	55.7784	8	3550.31	56.1228	9	3498.24	58.9635	10	3449.06	59.0499
11	3423.03	58.5618	12	3395.07	63.0363	13	3319.86	64.5412	14	3238.86	67.8824	15	3175.22	67.3832
16	2952.48	68.9616	17	2920.66	72.1256	18	2571.61	92.2659	19	2372.98	89.0695	20	2322.84	87.0096
21	2107.81	90.3105	22	1731.76	69.1465	23	1633.41	87.4424	24	1469.49	76.7396	25	1397.17	65.3772
26	1141.65	73.2679	27	962.305	87.8586	28	904.451	88.5351	29	847.561	81.3847	30	806.099	87.22
31	756.923	75.6917	32	593.968	87.4538	33	566.005	83.6015	34	503.33	74.6305	35	465.725	66.9545
36	431.977	87.1022												

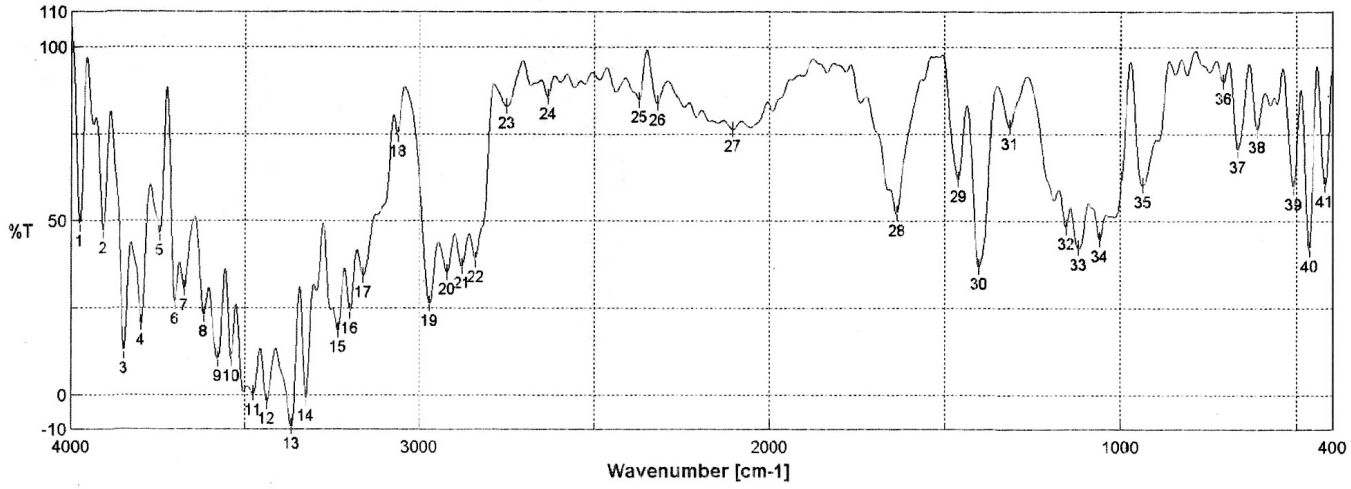
Figure: 8 IR Spectrum of EC



Accumulation	16	Resolution	4 cm-1
Zero Filling	ON	Apodization	Cosine
Gain	8	Scanning Speed	2 mm/sec
Date/Time	12/6/2007 11:19AM	Update	1/4/2008 3:59PM
Operator	C.Geetha		
File Name	EC		
Sample Name	EC		
Comment			

No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T
1	3910.93	81.539	2	3818.36	84.3084	3	3741.23	74.1339	4	3677.59	77.9297	5	3604.3	63.9551
6	3498.24	56.9265	7	3240.79	73.5824	8	2975.62	68.5599	9	2873.42	70.7767	10	1746.23	84.5748
11	1645.95	85.4964	12	1398.14	55.3937	13	1117.55	55.2849	14	918.914	90.453	15	877.452	87.2766
16	802.242	92.1251	17	600.717	78.2458	18	491.759	80.1032	19	417.513	45.0263			

Figure: 9 IR Spectrum of HPMC

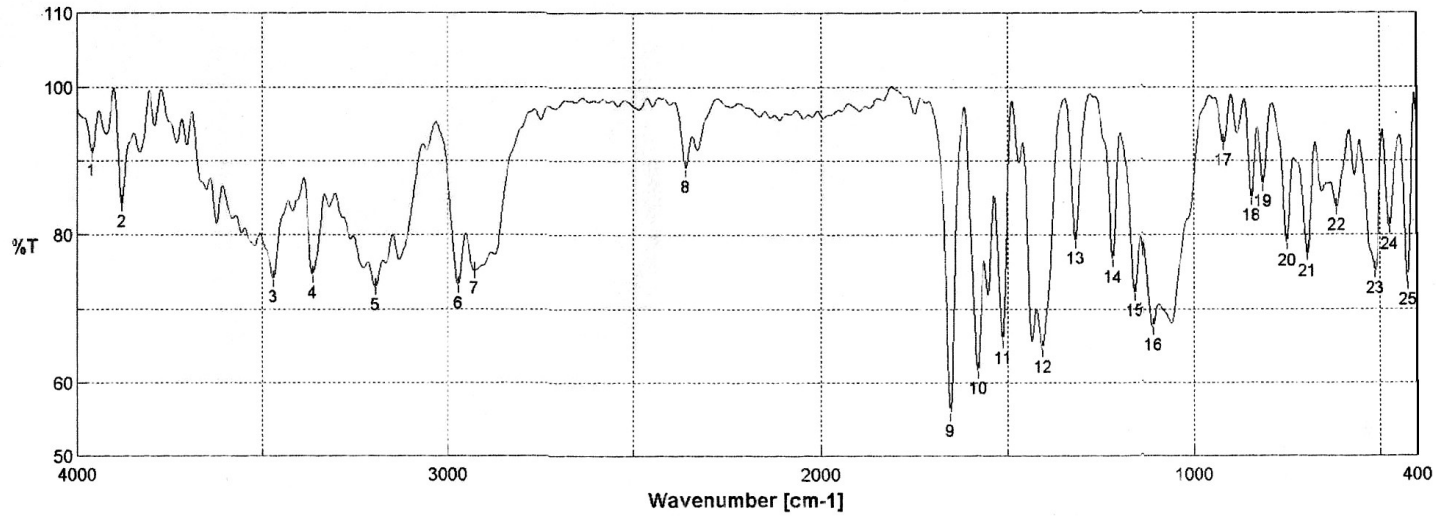


Accumulation	16
Zero Filling	ON
Gain	32
Date/Time	12/6/2007 11:13AM
Operator	C.Geetha
File Name	HPMC
Sample Name	HPMC
Comment	

Resolution	4 cm-1
Apodization	Cosine
Scanning Speed	2 mm/sec
Update	1/4/2008 4:07PM

No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T
1	3975.53	48.907	2	3909	47.0846	3	3847.29	12.3759	4	3796.19	20.5036	5	3741.23	46.3179
6	3697.84	26.6374	7	3670.84	30.5854	8	3614.91	22.9883	9	3576.34	10.1902	10	3538.74	10.1349
11	3476.06	0.349384	12	3437.49	-2.05621	13	3365.17	-9.02671	14	3322.75	-1.21273	15	3231.15	18.5893
16	3196.43	24.0174	17	3159.79	34.2767	18	3063.37	74.701	19	2970.8	26.1814	20	2920.66	35.2191
21	2877.27	36.9449	22	2837.74	38.8857	23	2748.07	82.9002	24	2634.29	85.6128	25	2370.09	84.8049
26	2318.02	83.7781	27	2106.85	76.3214	28	1639.2	52.0126	29	1459.85	61.8941	30	1399.1	36.8657
31	1316.18	76.918	32	1157.08	48.3419	33	1120.44	42.3123	34	1058.73	44.7361	35	938.199	60.3458
36	709.676	89.9877	37	667.25	70.389	38	612.288	76.1028	39	508.151	59.6487	40	464.761	41.8312
41	421.37	60.6075												

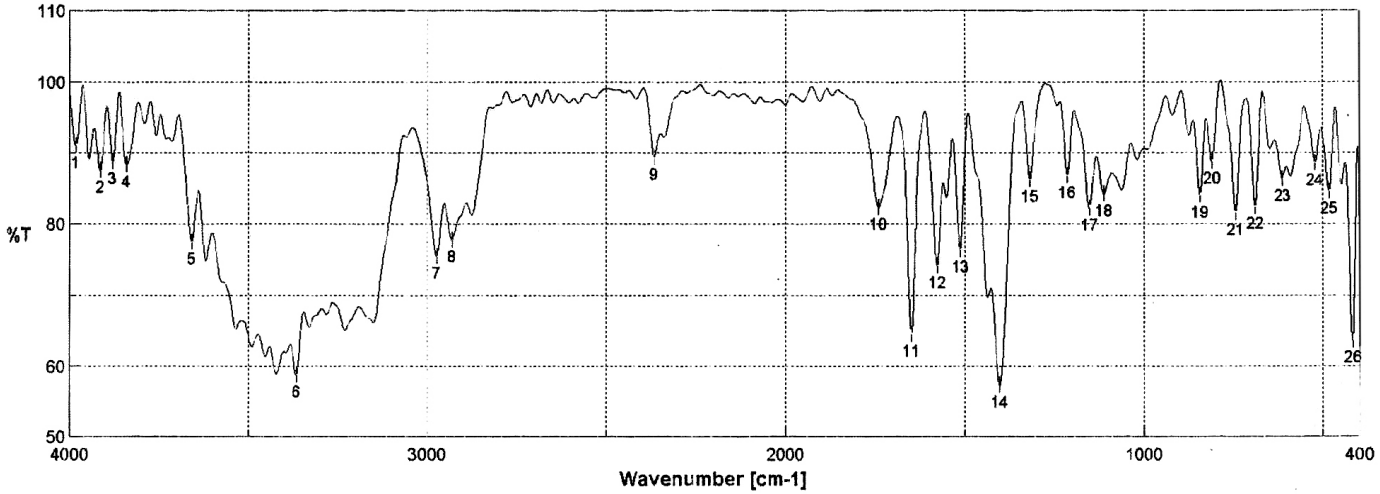
Figure: 10 IR Spectrum of Drug + HPMC + EC



Accumulation	16	Resolution	4 cm-1
Zero Filling	ON	Apodization	Cosine
Gain	8	Scanning Speed	2 mm/sec
Date/Time	12/6/2007 11:34AM	Update	1/4/2008 4:09PM
Operator	C.Geetha		
File Name	HPMC-EC		
Sample Name	HPMC-EC		
Comment			

No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T
1	3959.14	91.0921	2	3878.15	84.273	3	3470.28	74.0891	4	3364.21	74.6673	5	3198.36	72.9554
6	2972.73	73.1871	7	2929.34	75.16	8	2361.41	88.9544	9	1650.77	55.8579	10	1579.41	61.6711
11	1512.88	65.7727	12	1404.89	64.5619	13	1315.21	79.2968	14	1216.86	76.6831	15	1157.08	72.1604
16	1110.8	67.5322	17	916.986	92.4625	18	841.776	85.061	19	810.92	86.9538	20	748.245	78.9369
21	693.284	77.4921	22	616.145	83.706	23	512.008	75.1342	24	473.439	81.1303	25	425.227	73.6069

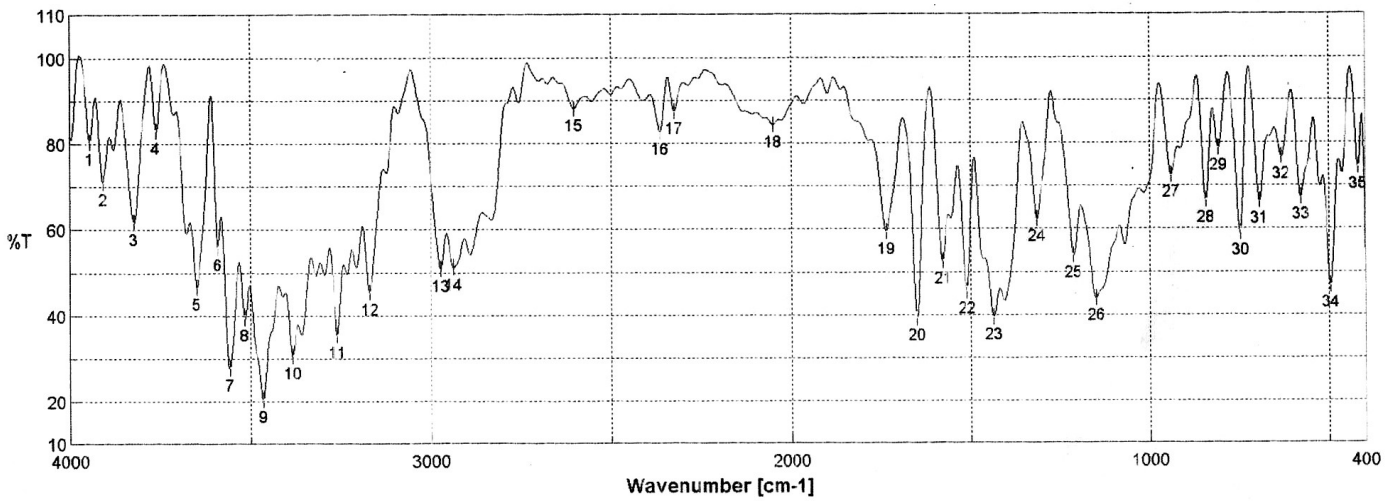
Figure: 11 IR spectrum of Drug + EC + ERS100



Accumulation	16	Resolution	4 cm-1
Zero Filling	ON	Apodization	Cosine
Gain	8	Scanning Speed	2 mm/sec
Date/Time	12/6/2007 11:45AM	Update	1/4/2008 4:03PM
Operator	C.Geetha		
File Name	EC-ERS		
Sample Name	EC-ERS		
Comment			

No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T
1	3983.25	91.0279	2	3916.72	87.5425	3	3882	88.8054	4	3842.47	88.3771	5	3657.34	77.4557
6	3386.14	58.7887	7	2974.66	75.5017	8	2930.31	77.8821	9	2363.34	89.3882	10	1740.44	82.3496
11	1650.77	64.5574	12	1579.41	74.1578	13	1512.88	76.3407	14	1399.1	57.2855	15	1315.21	86.3098
16	1215.9	86.7791	17	1155.15	82.3009	18	1114.65	84.231	19	844.669	84.0891	20	811.885	88.8489
21	747.281	81.6213	22	692.32	82.529	23	615.181	86.3426	24	520.686	88.5918	25	482.117	84.6238
26	418.477	63.6293												

Figure: 12 IR Spectrum of Drug + HPMC + E RS100



Accumulation	16	Resolution	4 cm-1
Zero Filling	ON	Apodization	Cosine
Gain	16	Scanning Speed	2 mm/sec
Date/Time	12/6/2007 11:40AM	Update	1/4/2008 4:13PM
Operator	C.Geetha		
File Name	HPMC-ERS		
Sample Name	HPMC-ERS		
Comment			

No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T
1	3945.64	80.4411	2	3909.97	71.0092	3	3825.11	61.8192	4	3762.44	82.9722	5	3647.7	46.591
6	3588.88	55.8788	7	3556.09	27.8128	8	3514.63	39.3131	9	3465.46	20.3913	10	3385.42	30.4875
11	3262	35.4059	12	3169.44	45.28	13	2973.7	50.8346	14	2938.02	51.2273	15	2602.47	88.1881
16	2363.34	82.5585	17	2323.8	87.4394	18	2051.89	84.337	19	1736.58	59.3859	20	1650.77	39.2892
21	1579.41	52.4989	22	1510.95	45.5206	23	1433.82	39.4465	24	1315.21	62.291	25	1214.93	53.7689
26	1152.26	43.7395	27	939.163	72.5326	28	844.669	66.5768	29	808.992	78.7632	30	748.245	58.958
31	693.284	66.3497	32	631.573	76.6833	33	577.576	67.2322	34	495.616	46.7785	35	420.406	74.3838

Physico- Chemical parameters

Twenty-one patches of Atorvastatin calcium loaded with different ratios of HPMC, EC and ERS100 were prepared by moulding technique. The prepared patches were evaluated for physico chemical parameters and in vitro drug release behaviour.

The determination of the average weight of patch, having 15.21cm^2 surface area showed a significant change between the patches prepared with different polymer ratios. The average weight of the patches T_1- T_{21} were given in the table: 6-8. Among the 21 patches, T_1- T_7 showed a higher average weight compared to other patches and T_{15}-T_{21} showed less weight. This increase in weight of T_1- T_7 patches is due to usage of 10%w/w of polymers whereas in other formulations only 5%w/w polymers were used.

There was no significant change in the thickness of the patches (T_1-T_{21}), which was determined by aerospace digital electronic micrometer (table: 6-8). This indicates that the patches were uniform and reproducible.

The results of moisture content (table: 6-8) of the coded transdermal patches (T_8-T_{14}) showed a marked difference in the moisture content. The patches T_8-T_{21} showed higher moisture content and moisture uptake, which was due to the higher content of hydrophilic polymer, HPMC. The patches T_1 to T_7 showed less moisture content and uptake because of the blend of both hydrophobic polymers.

Tensile strength (table: 6-8) is found to be higher for the patches T_8-T_{15} when compared to other patches and hardness (table: 9) is found to be low for the patches T_8-T_{15} when compared to other patches.

All the patches showed uniform drug content, which was determined using SHIMADZU UV- 1700 spectrophotometer (table: 6-8).

Table: 6 Physico-chemical parameters of the formulated transdermal patches of Atorvastatin calcium- T_1 to T_7

Formulation Code	Polymer Ratio EC: ERS100	Physical Appearance	Weight Variation (grams)	Thickness (mm)	Tensile Strength (kg/cm^2)	Moisture Content (%)	Moisture Uptake (%)	Drug Content (mg/cm^2)
T1	4.5:0.5	Translucent, Flexible, Smooth.	0.592±0.028	0.175±0.009	0.946	3.31±0.18	5.43±0.01	0.5969
T2	4:1	Translucent, Flexible, Smooth.	0.566±0.017	0.184±0.013	0.927	2.77±0.16	4.97±0.004	0.547
T3	3.5:1.5	Translucent, Flexible, Smooth.	0.474±0.019	0.147±0.003	0.945	2.59±0.43	4.05±0.001	0.6449
T4	3:2	Translucent, Flexible, Smooth.	0.500±0.009	0.152±0.008	0.943	2.48±0.90	3.77±0.009	0.5437
T5	2.5:2.5	Translucent, Flexible, Smooth.	0.497±0.01	0.167±0.006	0.895	2.43±0.66	3.15±0.01	0.6219
T6	2:3	Translucent, Flexible, Smooth.	0.502±0.008	0.195±0.018	0.839	2.09±0.49	2.64±0.02	0.6002
T7	1:4	Translucent, Flexible, Smooth.	0.525±0.001	0.056±0.043	0.890	1.24±0.57	1.99±0.025	0.5739

Table No: 7 Physico-chemical parameters of the formulated transdermal patches of Atorvastatin calcium- T_8 to T_{14}

Formulation Code	Polymer Ratio HPMC: EC	Physical Appearance	Weight Variation (grams)	Thickness (mm)	Tensile Strength (kg/cm^2)	Moisture Content (%)	Moisture Uptake (%)	Drug Content (mg/cm^2)
T8	4.5:0.5	Transparent, Flexible, Smooth	0.322±0.006	0.157±0.015	1.755	8.75±0.015	10.12±0.006	0.5634
T9	4:1	Transparent, Flexible, Smooth	0.322±0.006	0.120±0.07	1.645	7.55±0.007	9.88±0.009	0.5456
T10	3.5:1.5	Transparent, Flexible, Smooth	0.327±0.008	0.119±0.001	1.599	7.09±0.017	8.98±0.013	0.5391
T11	3:2	Transparent, Flexible, Smooth	0.304±0.005	0.102±0.008	1.555	6.63±0.002	8.17±0.016	0.5128
T12	2.5:2.5	Transparent, Flexible, Smooth	0.284±0.008	0.084±0.016	1.60	5.88±0.01	7.76±0.035	0.5542
T13	2:3	Transparent, Flexible, Smooth	0.293±0.005	0.134±0.005	1.504	5.14±0.03	6.85±0.048	0.6101
T14	1:4	Transparent, Flexible, Smooth.	0.286±0.008	0.135±0.006	1.551	4.36±0.009	5.67±0.009	0.6239

Table No: 8 Physico-chemical parameters of the formulated transdermal patches of Atorvastatin calcium- T_{15} to T_{21}

Formulation	Polymer	Physical	Weight	Thickness	Tensile	Moisture	Moisture	Drug

Code	Ratio HPMC: ERS100	Appearance	Variation (grams)	(mm)	Strength (kg/cm^2)	Content (%)	Uptake (%)	Content (mg/cm^2)
T15	4.5:0.5	Transparent, Flexible, Smooth	0.283±0.01	0.152±0.009	1.360	6.09±0.24	7.51±0.017	0.6134
T16	4:1	Transparent, Flexible, Smooth	0.318±0.001	0.150±0.008	1.247	5.77±0.009	6.93±0.083	0.5654
T17	3.5:1.5	Transparent, Flexible, Smooth	0.310±0.001	0.112±0.017	1.389	4.98±0.017	6.22±0.037	0.5456
T18	3:2	Transparent, Flexible, Smooth	0.304±0.004	0.167±0.006	1.338	4.08±0.038	5.95±0.009	0.6173
T19	2.5:2.5	Transparent, Flexible, Smooth	0.337±0.009	0.188±0.016	1.287	3.56±0.061	5.28±0.044	0.5765
T20	2:3	Transparent, Flexible, Smooth	0.289±0.01	0.150±0.008	1.241	2.83±0.17	4.53±0.006	0.5351
T21	1:4	Transparent, Flexible, Smooth.	0.361±0.02	0.144±0.003	1.124	2.14±0.19	3.45±0.002	0.6213

Table: 9 HARDNESS PROFILE OF THE FORMULATED PATCHES-T_1 to T_{21}

Formulation code	Hardness (grams)	Formulation code	Hardness (grams)	Formulation code	Hardness (grams)
T_1	175	T_8	12.76	T_{15}	44
T_2	172	T_9	16.59	T_{16}	49
T_3	170	T_{10}	19.33	T_{17}	54
T_4	169	T_{11}	20.33	T_{18}	47
T_5	155	T_{12}	21.20	T_{19}	51
T_6	134	T_{13}	19.32	T_{20}	54
T_7	110	T_{14}	18.02	T_{21}	60

In vitro drug release studies

The in vitro drug release studies carried out indicate the influence of polymers on the release of drug. The cumulative release of drug (mg/cm^2) and cumulative percentage release of T_1- T_{21} patches over 24 hrs were determined and are summarized in table:11-16 and graph: 14-16.

The increase in HPMC concentration resulted in increase in drug released from T_8 patch, whereas T_1 showed lower drug release because both the polymers EC and ERS100 were hydrophilic. Patch T_{15} showed lesser release than T_8 because of the presence of hydrophobic polymer ERS100.

Skin irritation studies

The skin irritation study reveals that the drug loaded and unloaded patches didn't cause any noticeable signs of irritation or oedema on albino rat's skin, indicating the skin compatibility of drug as well as polymer matrix.

Stability studies

The stability studies indicate there was no change in physico-chemical and in vitro drug release studies for T_1, T_8, and T_{15} patches (table:17-19 & graph: 17).

Table: 10 Calibration graph of Atorvastatin calcium

SI. No.	Concentration mcg/ml	Absorbance @ 241nm
1.	4	0.155
2.	8	0.313
3.	12	0.468
4.	16	0.621
5.	20	0.774

Figure: 13 Calibration graph of Atorvastatin calcium

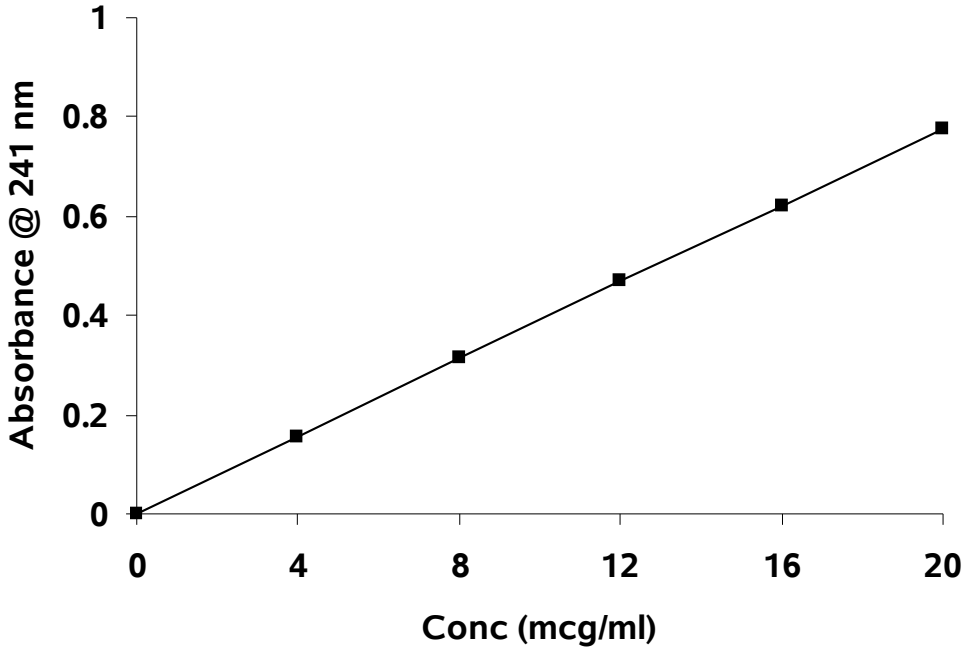


Table: 11 Cumulative amount release of atorvastatin calcium transdermal patches formulated by employing polymers like EC & ERS100: T_1 TO T_7

Polymer ratio EC:ERS 100	Cumulative amount release (mg/cm^2) of drug at										
	1 h	2 h	3 h	4 h	5 h	6 h	7 h	8 h	9 h	10 h	24 h
4.5:0.5	0.1058	0.0161	0.0193	0.0230	0.0271	0.0446	0.0501	0.0552	0.0612	0.0662	0.1546
4:1	0.0087	0.0110	0.0142	0.0179	0.0225	0.0253	0.0294	0.0354	0.0391	0.0465	0.1298
3.5:1.5	0.0092	0.0119	0.0133	0.0161	0.0197	0.0230	0.0276	0.0326	0.0368	0.0409	0.1159
3:2	0.0059	0.0110	0.0119	0.0170	0.0216	0.0243	0.0276	0.0322	0.0354	0.0386	0.1077
2.5:2.5	0.0023	0.0055	0.0078	0.0115	0.0152	0.0188	0.0225	0.0266	0.0308	0.0335	0.1022
2:3	0.0013	0.0036	0.0087	0.0124	0.0156	0.0197	0.0230	0.0262	0.0294	0.0326	0.0911
1:4	0.0005	0.0023	0.0059	0.0096	0.0119	0.0161	0.0197	0.0234	0.0262	0.0299	0.0690

Table: 12 Cumulative percentage release of atorvastatin calcium transdermal patches formulated by employing polymers like EC & ERS100: T_1 TO T_7

Polymer ratio EC:ERS 100	Cumulative percentage release of drug at										
	1 h	**2 h**	**3 h**	**4 h**	**5 h**	**6 h**	**7 h**	**8 h**	**9 h**	**10 h**	**24 h**
4.5:0.5	1.77	2.69	3.23	3.85	4.55	7.47	8.40	9.25	10.25	11.10	25.90
4:1	1.59	2.01	2.60	3.28	4.12	4.62	5.38	6.47	7.15	8.49	23.72
3.5:1.5	1.42	1.85	2.06	2.49	3.06	3.56	4.28	5.06	5.70	6.35	17.98
3:2	1.10	2.03	2.20	3.13	3.97	4.48	5.07	5.92	6.51	7.11	19.80
2.5:2.5	0.37	0.88	1.25	1.84	2.44	3.03	3.62	4.29	4.95	5.40	16.42
2:3	0.23	0.61	1.45	2.07	2.60	3.29	3.83	4.37	4.90	5.44	15.18
1:4	0.08	0.40	1.04	1.68	2.08	2.80	3.44	4.08	4.57	5.21	12.02

Figure: 14 INVITRO RELEASE PROFILE OF PATCHES T_1 TO T_7

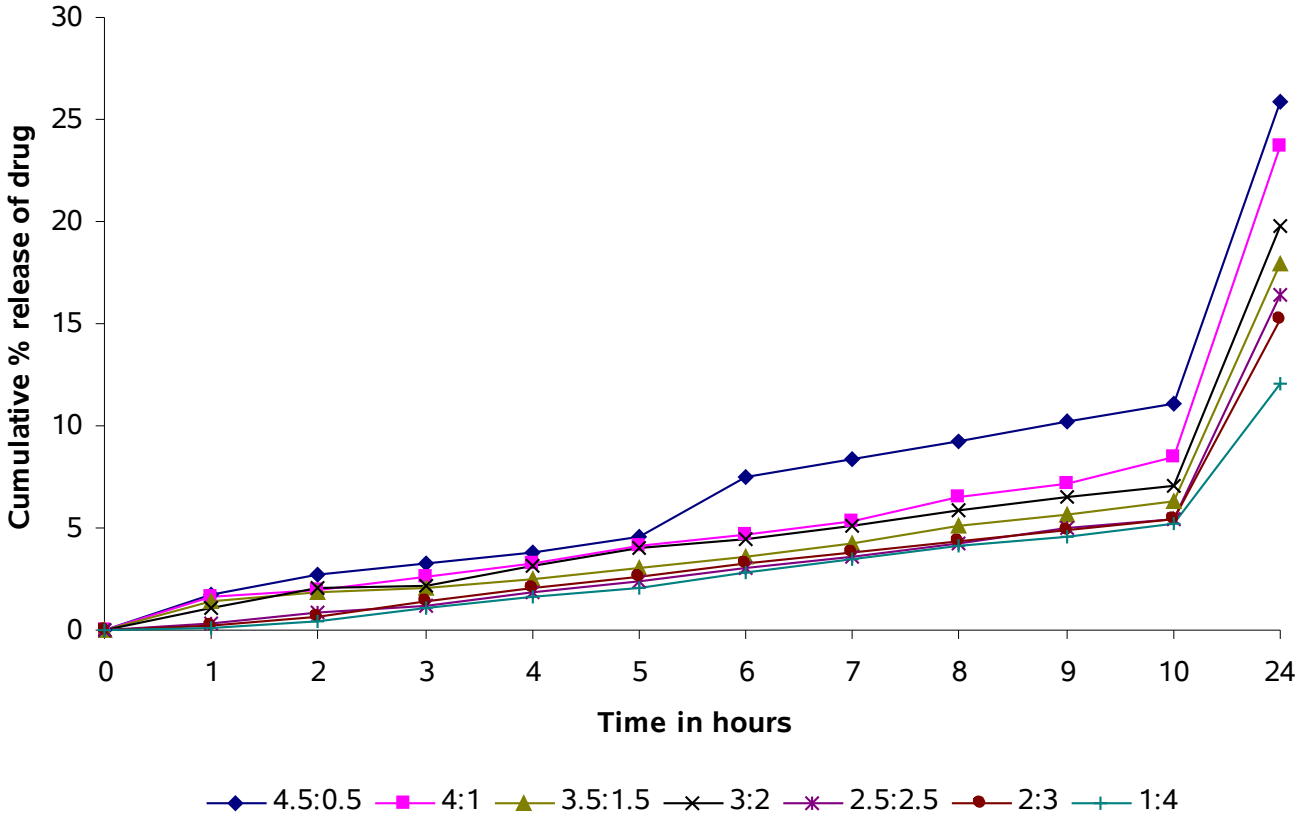


Table: 13 Cumulative amount release of atorvastatin calcium transdermal patches formulated by employing polymers like HPMC & EC: T_8 TO T_{14}

Polymer ratio HPMC:EC	Cumulative amount release (mg/cm^2) of drug at										
	1 h	2 h	3 h	4 h	5 h	6 h	7 h	8 h	9 h	10 h	24 h
4.5:0.5	0.0262	0.0349	0.0579	0.0685	0.0814	0.0902	0.1031	0.1380	0.1592	0.1739	0.4832
4:1	0.0211	0.0326	0.0464	0.0625	0.0786	0.0837	0.0984	0.1090	0.1491	0.1702	0.4556
3.5:1.5	0.0117	0.0331	0.0460	0.0520	0.0639	0.0736	0.0828	0.0902	0.1040	0.1187	0.4086
3:2	0.0138	0.0308	0.0414	0.0511	0.0598	0.0662	0.0745	0.0851	0.1003	0.1109	0.3835
2.5:2.5	0.0092	0.0142	0.0308	0.0404	0.0492	0.0612	0.0713	0.0768	0.0934	0.0952	0.356
2:3	0.0055	0.0110	0.0138	0.0340	0.0442	0.0547	0.0598	0.0823	0.0856	0.0943	0.348
1:4	0.0018	0.0027	0.0216	0.0312	0.0377	0.0478	0.0556	0.0648	0.0740	0.0860	0.3285

Table: 14 Cumulative percentage release of atorvastatin calcium transdermal patches formulated by employing polymers like HPMC & EC: T_8 TO T_{14}

Polymer ratio HPMC:EC	Cumulative percentage release of drug at										
	1 h	**2 h**	**3 h**	**4 h**	**5 h**	**6 h**	**7 h**	**8 h**	**9 h**	**10 h**	**24 h**
4.5:0.5	4.65	6.20	10.29	12.17	14.45	16.01	18.29	24.50	28.26	30.87	85.77
4:1	3.88	5.98	8.51	11.47	14.42	15.35	18.05	19.99	27.32	31.21	83.56
3.5:1.5	2.21	6.14	8.53	9.64	11.8	13.65	15.36	16.73	19.29	22.02	75.80
3:2	2.69	6.01	8.07	9.96	11.66	12.92	14.54	16.60	19.56	21.62	74.78
2.5:2.5	1.66	2.57	5.56	7.30	8.88	11.64	12.87	13.86	16.85	17.19	64.27
2:3	0.95	1.81	2.26	5.58	7.24	8.97	9.80	13.50	14.03	15.46	57.02
1:4	0.29	0.44	3.46	5.01	6.04	7.67	8.92	10.40	11.87	13.79	52.66

Figure: 15 INVITRO RELEASE PROFILE OF PATCHES T_8 TO T_{14}

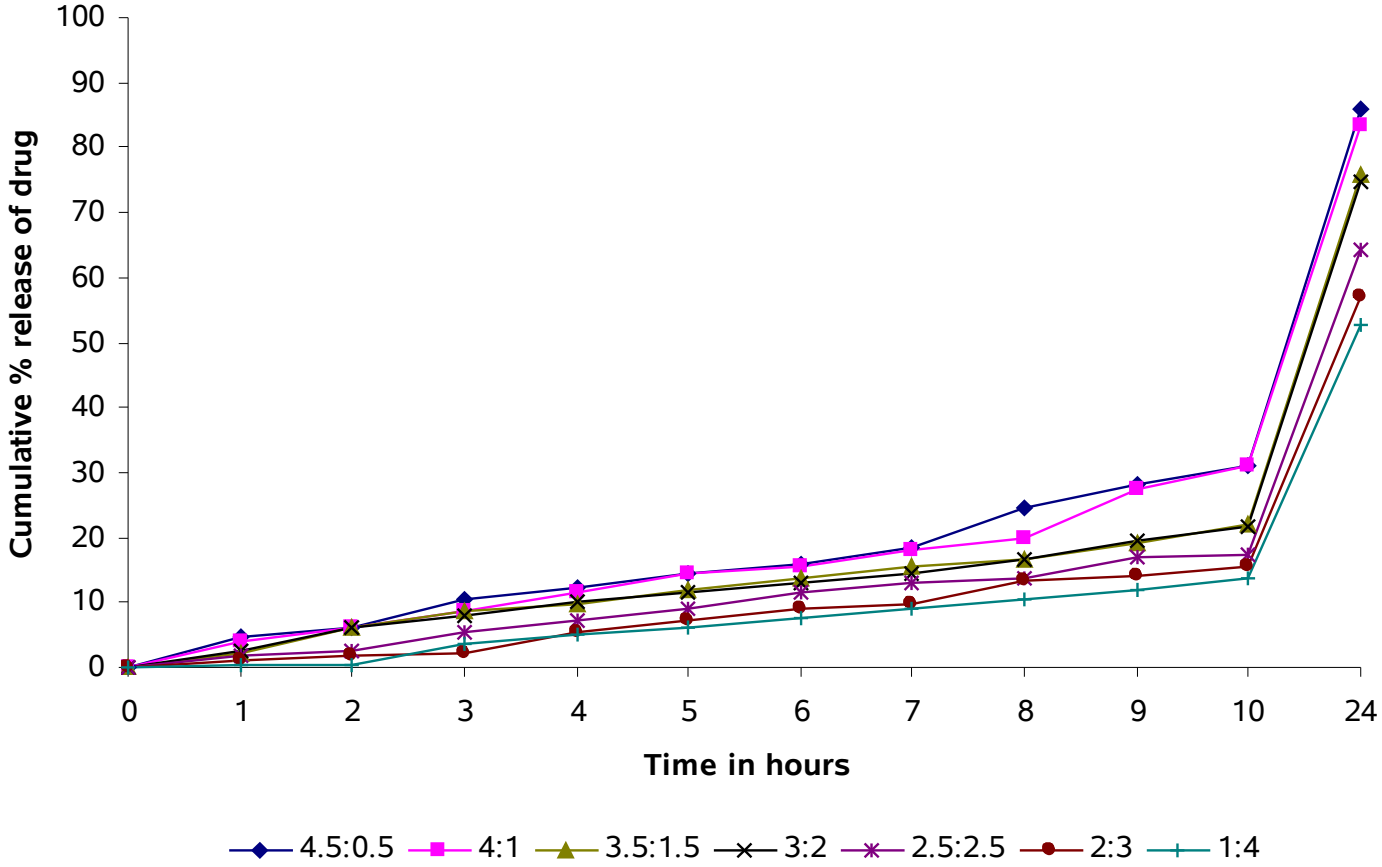


Table: 15 Cumulative amount release of Atorvastatin calcium transdermal patches formulated by employing polymers like HPMC & ERS100: T_{15} TO T_{21}

Polymer ratio HPMC:ERS 100	Cumulative amount release (mg/cm^2) of drug at										
	1 h	2 h	3 h	4 h	5 h	6 h	7 h	8 h	9 h	10 h	24 h
4.5:0.5	0.0188	0.0294	0.0464	0.0570	0.0667	0.0740	0.0828	0.0920	0.1003	0.1182	0.2927
4:1	0.0119	0.0253	0.0354	0.0409	0.0511	0.0662	0.0736	0.0824	0.0888	0.0957	0.2706
3.5:1.5	0.0152	0.0230	0.0262	0.0359	0.0492	0.0612	0.0708	0.0759	0.0860	0.0948	0.2623
3:2	0.0096	0.0156	0.0248	0.0359	0.0409	0.0570	0.0639	0.0708	0.0768	0.0842	0.2402
2.5:2.5	0.0069	0.0101	0.0129	0.0225	0.0289	0.0368	0.0474	0.0520	0.0607	0.0732	0.2236
2:3	0.0041	0.0073	0.0115	0.0142	0.0239	0.0308	0.0382	0.0465	0.0570	0.0667	0.1795
1:4	0.0018	0.0050	0.0101	0.0128	0.0188	0.0248	0.0345	0.0428	0.0566	0.0589	0.162

Table: 16 Cumulative percentage release of Atorvastatin calcium transdermal patches formulated by employing polymers like HPMC & ERS100: T_{15} TO T_{21}

Polymer ratio HPMC:ERS 100	Cumulative percentage release of drug at										
	1 h	**2 h**	**3 h**	**4 h**	**5 h**	**6 h**	**7 h**	**8 h**	**9 h**	**10 h**	**24 h**
4.5:0.5	3.07	4.80	7.57	9.30	10.88	12.07	13.50	15.00	16.35	19.28	47.71
4:1	2.11	4.47	6.26	7.24	9.03	11.72	13.02	14.57	15.71	16.93	47.86
3.5:1.5	2.78	4.21	4.80	6.57	9.02	11.21	12.99	13.92	15.77	17.37	48.08
3:2	1.56	2.53	4.02	5.81	6.63	9.24	10.36	11.48	12.45	13.64	38.92
2.5:2.5	1.19	1.75	2.23	3.91	5.03	6.38	8.22	9.02	10.54	12.69	38.79
2:3	0.77	1.37	2.15	2.66	4.47	5.97	7.14	8.68	10.66	12.47	33.54
1:4	0.29	0.81	1.62	2.07	3.03	4.00	5.55	6.88	8.15	9.48	26.22

Figure: 16 INVITRO RELEASE PROFILE OF PATCHES T_{15} TO T_{21}

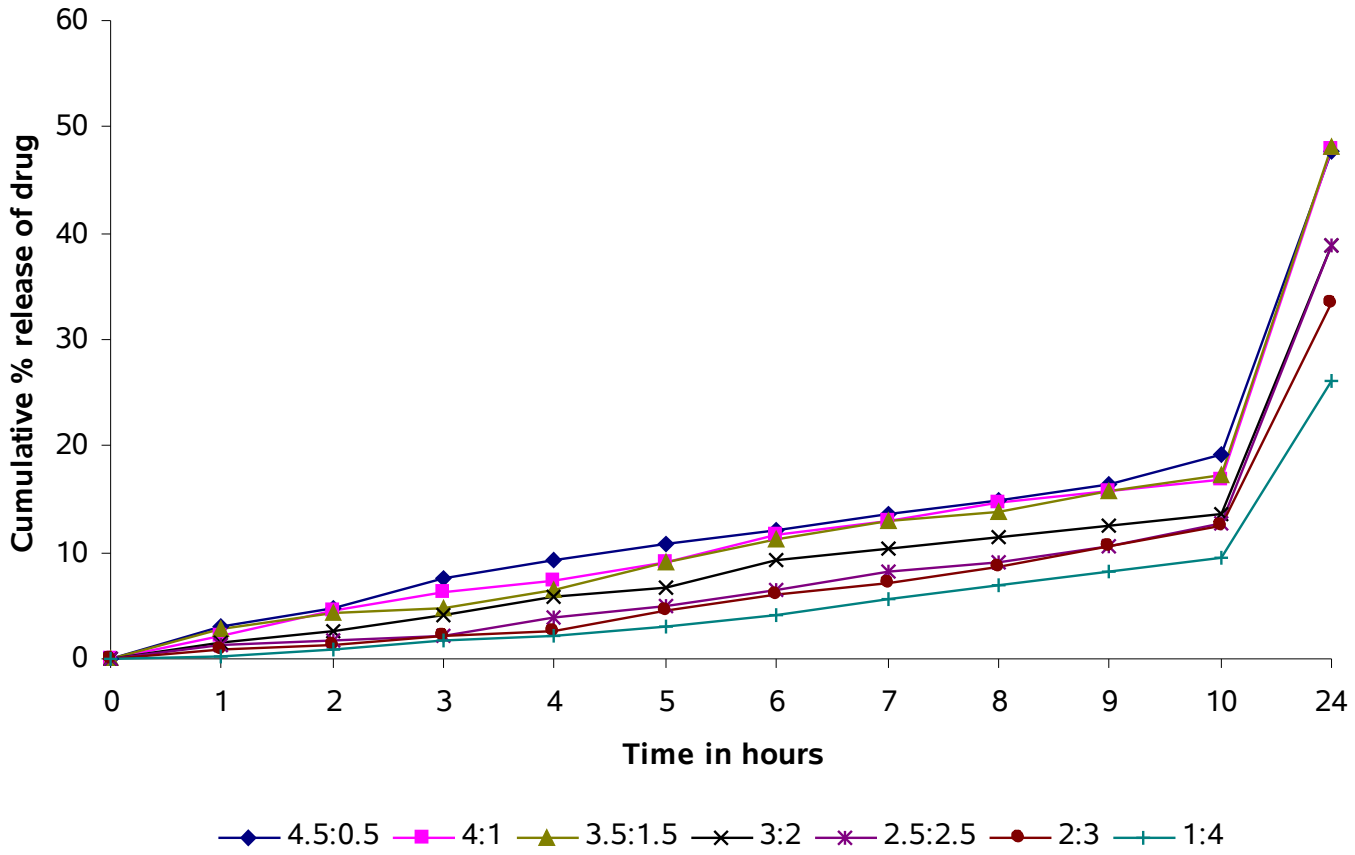

Cumulative % release of drug
60
50
40
30
20
10
0
0
1
2
3
4
5
6
7
8
9
10
24
Time in hours
4.5:0.5
4:1
3.5:1.5
3:2
2.5:2.5
2:3
1:4

Table:17 Physico-chemical evaluation of the developed transdermal patch (t_1) of atorvastatin calcium during the stability studies at 40°C

Time in days	Physical Appearance	Weight Variation (grams)	Thickness (mm)	Moisture Content (%)	Moisture Uptake (%)	Drug Content (mg/cm^2)	Cumulative amount release (mg/cm^2) at 24 h	Cumulative percentage release at 24 h
0	Translucent, Flexible, Smooth	0.589±0.012	0.178±0.005	3.05±0.009	5.29±0.025	0.5864	0.1546	26.36
15	No change	0.592±0.014	0.180±0.007	3.12±0.015	5.75±0.019	0.5862	0.1553	26.49
20	No change	0.590±0.009	0.181±0.005	3.17±0.010	5.93±0.013	0.5860	0.1539	26.26
45	No change	0.594±0.011	0.184±0.009	3.21±0.011	6.01±0.028	0.5965	0.1525	25.56

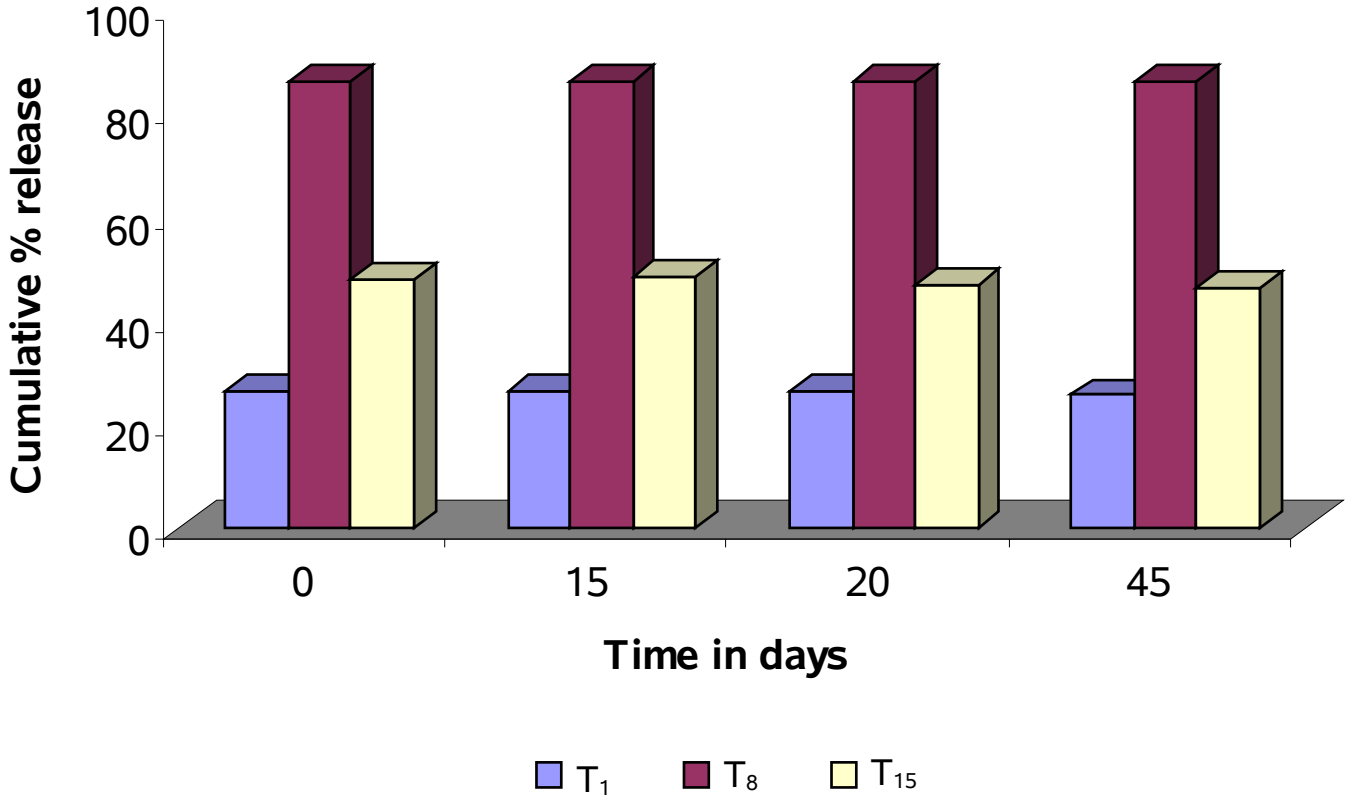
Table:18 Physico-chemical evaluation of the developed transdermal patch (t_8) of atorvastatin calcium during the stability studies at 40ºC

Time in days	Physical Appearance	Weight Variation (grams)	Thickness (mm)	Moisture Content (%)	Moisture Uptake (%)	Drug Content (mg/cm^2)	Cumulative amount release (mg/cm^2) at 24 h	Cumulative percentage release at 24 h
0	Transparent, Flexible, Smooth	0.322±0.006	0.157±0.015	8.75±0.015	10.12±0.006	0.5634	0.4832	85.77
15	No change	0.327±0.015	0.158±0.009	8.81±0.005	10.41±0.014	0.5637	0.4835	85.77
20	No change	0.330±0.009	0.161±0.004	8.97±0.03	10.73±0.023	0.5628	0.4828	85.78
45	No change	0.383±0.018	0.165±0.002	9.35±0.027	11.24±0.025	0.5619	0.4818	85.74

Table:19 Physico-chemical evaluation of the developed transdermal patch (t_{15}) of atorvastatin calcium during the stability studies at 40ºC

Time in days	Physical Appearance	Weight Variation (grams)	Thickness (mm)	Moisture Content (in %)	Moisture Uptake (%)	Drug Content (mg/cm^2)	Cumulative amount release (mg/cm^2) at 24 h	Cumulative percentage release at 24 h
0	Transparent, Flexible, Smooth	0.283±0.015	0.452±0.009	6.09±0.24	7.51±0.017	0.6134	0.2927	47.71
15	No change	0.291±0.023	0.154±0.016	5.98±0.004	7.71±0.12	0.5982	0.2903	48.52
20	No change	0.299±0.017	0.147±0.31	6.25±0.009	7.98±0.14	0.6121	0.2875	46.96
45	No change	0.303±0.028	0.15±0.042	6.92±0.17	8.32±0.25	0.6104	0.2821	46.21

Figure:17 Comparative cumulative percentage release of transdermal patches T1, T8 and T15 during stability studies at 40ºC


Cumulative % release
100
80
60
40
20
0
0
15
20
45
Time in days
T1
T8
T15

SUMMARY AND CONCLUSION

An attempt to develop transdermal therapeutic system for Atorvastatin calcium using polymers like HPMC, EC, and ERS100 was carried out for the purpose of attaining maximum bioavailability by tress passing pre-systemic hepatic metabolism.

The compatibility studies using TLC and IR spectral studies revealed the absence of interaction between the drug and the polymer.

The formulated patches were evaluated for the physico-chemical parameters, in vitro drug release studies, skin irritation studies and stability studies.

The patches showed a significant variation in their average weight, which might be due to the variation in the proportions of polymers used. There was no significant change observed in the thickness of all the twenty-one patches.

The percentage moisture content and percentage moisture uptake is found to be high for the patches formulated with HPMC:EC when compared to the patches formulated with HPMC:ERS100 and EC:ERS100. The reason behind the screen might be the higher proportions of hydrophilic polymer, HPMC along with EC; whereas patches with HPMC:ERS100 combination shows lesser moisture content and moisture uptake because of the highly hydrophobic polymer, ERS100.

For the patches with HPMC:EC tensile strength was found to be high and hardness was found to be low when compared to other patches which might be due to the nature of the polymers.

All the patches showed uniform drug content.

The formulations T_8-T_{14} showed a better in vitro drug release profile across the cellulose membrane, when compared to the other formulations. This might be attributed to the nature of polymer; plasticizers used and even the permeation enhancer.

The skin irritation studies using albino-rats revealed no signs of irritation or oedema, which confirms the skin compatibility of both the drug loaded and plain patches.

As far the above results where concerned formulations T_1, T_8, and T_{15} where selected and subjected for stability studies at room temperature and at 40ºC for a period of 45 days. The stability studies results signified that the formulated patches possess adequate shelf life till 45 days.

Since the results are encouraging for the formulation T_8, the proper technique should be applied for commercial and mass production of the same formulation.

However long term pharmacokinetic and pharmacodynamic studies should be undertaken to establish the usefulness of these patches.

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